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HEART MURMURS

PART I

BY

WILLIAM EVANS

From the Cardiac Department of the London Hospital

Received November 5, 1946

Auscultation of the heart, depending as it does on the acuity of the auditory sense and providing information commensurate with the observer's experience, cannot always determine unequivocally the various sound effects that may take place during systole and diastole. It is not surprising, therefore, that auscultation tied to traditional theories may sometimes lead to a wrong interpretation of the condition, although a judgment born of ripe experience in clinical medicine and pathology will avoid serious mistakes. It is more than fortuitous that modern auscultation has grown on such a secure foundation, but it is imperative that for the solution of outstanding problems there should be precise means of registering heart sounds. This is why a phonocardiogram was included in the examination of a series of patients presenting murmurs.

As each patient attended for the test, the signs elicited on clinical auscultation were first noted and an opinion was formed on their significance. Cardioscopy was invariably carried out, and, when necessary, teleradiograms were taken. Limb and chest lead electrocardiograms were frequently recorded in addition to the lead selected as a control for the phonocardiogram. Many cases came to necropsy. The simultaneous electrocardiogram and sound record was taken by a double string galvanometer supplied by the Cambridge Instrument Company, and the length of the connecting tube leading from the chest to the amplifier was 46 cm. Although the amplitude of sounds and murmurs was matched against each other in individual patients, there was no attempt to standardize the intensity of murmurs in terms of amplitude in different patients; in fact it was varied deliberately in order to produce such excursion of the recording fibre as would best show the murmur.

The actual place of the murmur in the cardiac cycle received first attention, and its intensity was only incidentally observed and noted. Before engaging in a phonocardiographic analysis of heart murmurs it is necessary to know the place occupied by each heart sound in the cardiac cycle as timed by the simultaneous electrocardiogram. In the physiological tracing obtained with a short connecting tube of 46 cm. the auricular moiety of the first heart sound begins at the end of the P wave of the electrocardiogram; occasionally it starts a little later, but never earlier. During the R–S period the auricular sound is reinforced abruptly by the ventricular moiety of the first heart sound. This combined sound effect is completed as a rule before the start of the T wave; at the end of the T wave the second heart sound starts (Fig. 1). After a brief interval the third heart sound is usually seen, and it is often obvious though inaudible on auscultation.

To simplify the location of murmurs in relation to the separate phases of the cardiac cycle it is well to draw a line through a point that marks the end of the S wave of the electrocardiogram and prolong it to intersect the phonocardiogram: this may be named the S line. A murmur that precedes the S line is the effect of auricular systole; if it starts at the S line

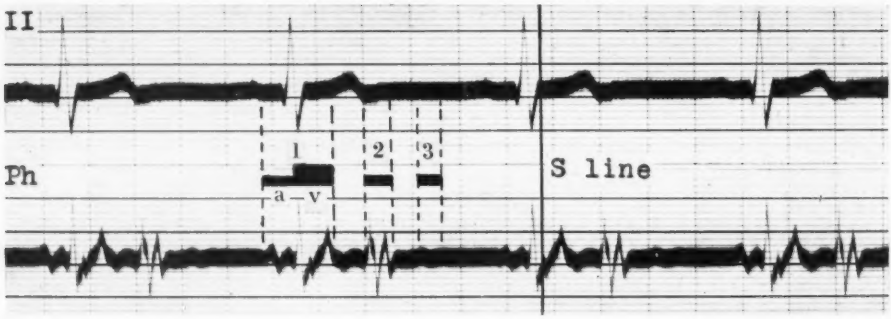

FIG. 1.—Normal phonocardiogram showing the heart sounds in relation to the electrocardiogram. The S line drawn at the end of the S wave of the electrocardiogram and continued to intersect the phonocardiogram, marks the early phase of ventricular contraction. The auricular (a) and ventricular (v) moieties of the first heart sound are shown, as well as the second (2) and third (3) heart sounds; the third was inaudible.

it coincides with the early phase of ventricular systole; if it starts a little later than the S line the murmur occupies mid-systole. Next the customary form of the graphic complex depicting the separate normal heart sounds should be studied in order that the variant produced by the addition of a murmur may be recognized. They differ one from the other only in the frequency of the vibration which creates them. Thus, the oscillations produced by a heart sound are fewer or coarser, those produced by a murmur are more numerous and finer—they bear the same relation to one another as the teeth of a coarse hair comb bears to a fine one (Fig. 2).

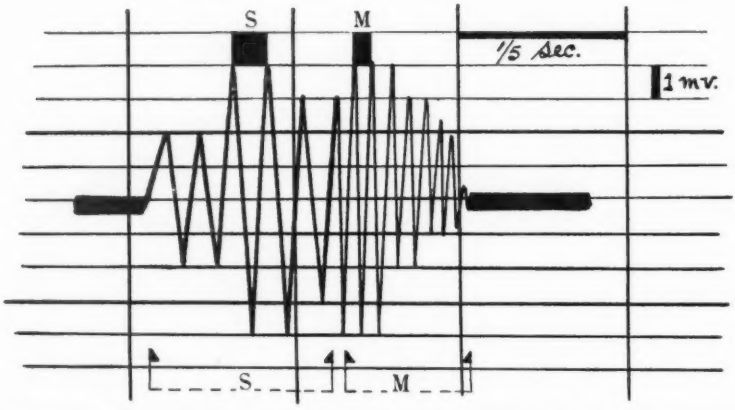

FIG. 2.—Diagrammatic representation of a heart sound (S) and murmur (M) in the phonocardiogram. The sound is a coarser vibration than the murmur, and the distance between each vibration forms a square in relation to the millimetre scale in the case of a heart sound and an oblong in the case of a murmur.

A phonocardiographic study of murmurs is fruitless unless it is closely linked with the clinical analysis of the patients concerned. The findings of this investigation, therefore, are discussed in relation to patients in seven main clinical groups, namely, healthy subjects, mitral valve disease, aortic valve disease, hypertension, congenital heart disease, heart block, and anæmia.

I. THE INNOCENT MURMURS

It has been traditional to speak of functional murmurs in the mitral area, but a search of the literature has shown a scarcity of observations on the characteristic features, apart from their quiet quality, that might identify such murmurs as the innocent kind. The need for such observations becomes obvious when clinical cardiology includes within its scope the examination of school-children whose playtime activities have been restricted and their early schooling neglected by non-attendance, recruits who have been denied military service and relegated to a low health category by medical boards, applicants for life insurance either rejected or accepted at increased premiums, and casual patients whose past health history recounts the handicap from restrictions imposed after examination of the heart—all because an insignificant murmur had been mistaken for one that indicates organic heart disease. Should this murmur be associated with " growing pains " or with a past history of rheumatic fever, the unjustified invalidism is more certain to be enforced. This uncertainty regarding individual mitral murmurs has imparted to them an ambiguity that has greatly hindered the diagnosis of cardiovascular disorders. It is clear, therefore, that identification of the *innocent* murmur, is as important, if not more important than the recognition of a murmur signifying disease and requires such specific clinical and graphic features as will make its diagnosis easier and surer.

Among patients attending the Cardiac Department of the London Hospital during four years there were 330 with an innocent mitral murmur. Care was taken to establish its benign nature, but naturally short of necropsy. A routine clinical examination followed a medical history, and special attention was paid to the site, intensity, length, and conduction of the murmur, and the effect of posture, respiration, and tachycardia upon it. Its position in the cardiac cycle, often difficult, was particularly sought, and the presence of a thrill was always tested. Diastolic murmurs were never present. An electrocardiogram was often taken whenever it might help to exclude certain organic disease, but as it never showed changes peculiar to the innocent group, it was not adopted as a routine. A selected lead was, of course, recorded to control the phonocardiogram whenever this was taken. Great reliance was placed on cardioscopy, which was used in every case and the progress of a barium swallow was watched in both oblique positions. Phonocardiography was applied frequently and as the investigation proceeded the features of the tracing could be predicted after clinical examination; such sound records were compared with those obtained from the mitral area in patients with heart disease.

Following the clinical and phonocardiographic examination it was found that although subjects with innocent murmurs could be conveniently separated into certain groups, the exact mechanism of the murmur could not be determined as neither the clinical nor the special examination provided a clue. The condition of the pericardium, mediastinum, lungs, pleura, and diaphragm was scrutinized during radiology of the chest, but this showed no obvious or consistent abnormality and failed to explain the source of the murmur. Even phonocardiography, which demonstrated the place of the murmur in relation to the cardiac cycle, did not disclose the mechanism. Necropsy in these subjects is awaited, although such an event would naturally be fortuitous; even then it is unlikely that the cause of the murmur would show. The fact that the mechanism of the innocent murmur is unexplained need not encourage conjecture on its ways of production, and must not delay the building of a clinical syndrome that might by itself decide the innocent nature of the murmur. Although the first grouping was on clinical grounds, phonocardiography later showed that these grounds were valid, hence great emphasis is given to sound records in this investigation.

The Murmurs in Mid-Systole

This was by far the commonest variety of innocent murmur and accounted for 262 of the 330 cases. It occurred with equal frequency in both sexes. The murmur was never rough nor harsh, but it could be described as roughish or blowing in character; very occasionally it was musical. The distinctive feature was the position of the murmur in mid-systole so that in the phonocardiogram (Fig. 3 and 4) it commenced a little way beyond the *S line* and did not last long. In this respect the tracing differed from the one obtained in mitral disease, where the murmur usually preceded the S line, starting within the P–R period (Fig. 5). Although

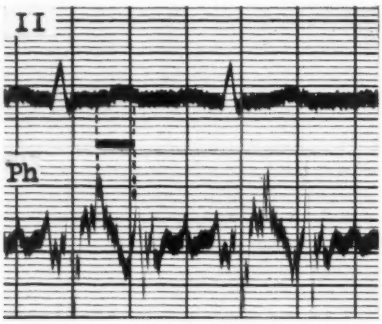

Fig. 3.—The innocent systolic murmur of reclining posture. In this and succeeding records the murmur is indicated by a black line, the start and finish of which is projected on to the electrocardiogram and phonocardiogram.

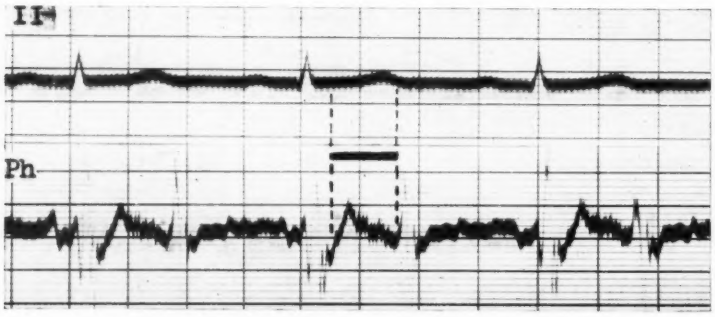

Fig. 4.—The innocent systolic murmur of upright posture.

it was not always possible, especially under the handicap of tachycardia, to establish the mid-systolic position of this murmur by auscultation, whenever a gap was detected between the first heart sound and the murmur following it, it was proof of its innocence. The corroborative test of phonocardiography, therefore, has been invaluable in establishing the validity of the clinical signs proposed for the identification of the separate varieties of innocent murmur.

Apart from its selective position in systole—slightly postponed in fact—which gives to this murmur its distinctive character, there were clinical features that decided by themselves its innocent nature even without a phonocardiogram. From a consideration of the site and intensity of the murmur, and the influence upon it of posture, it was found that the cases

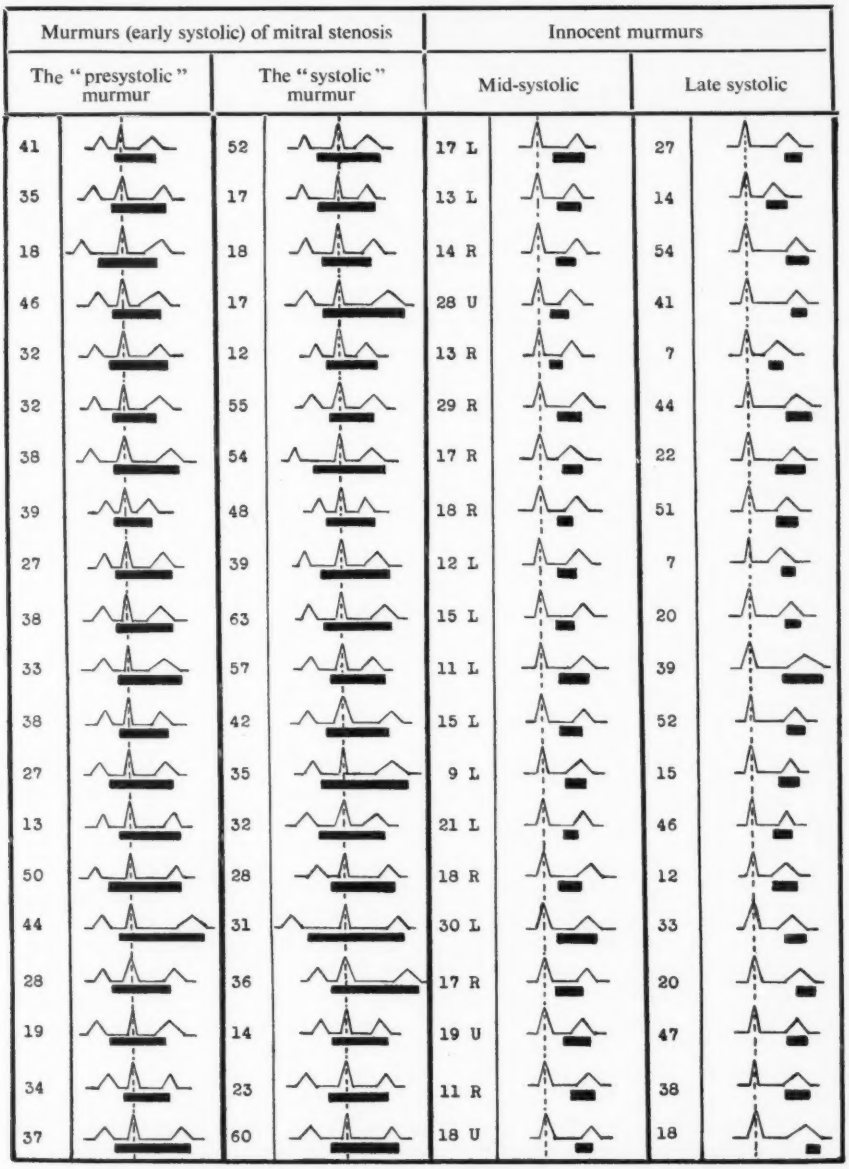

FIG. 5.—The position of mitral systolic murmurs (represented by black lines) in relation to the electrocardiogram in 40 patients with mitral stenosis (20 with a presystolic and 20 with a systolic murmur), and in 40 healthy subjects with innocent murmurs (20 with the murmur in mid-systole and 20 in late systole). Figures denote ages. Letters in the third column designate the clinical classification for innocent murmurs, thus, R is the murmur of Reclining Posture, U the murmur of Upright Posture, and L the Loud Variety.

could be allocated to four groups. The investigation has emphasized the importance of this clinical classification in the identification of this murmur, and the characteristic signs summarized in Table I, will now be described for each group. It bears repetition that the value of the phonocardiogram has so far been found not in its routine use for the detection of innocent murmurs, but to confirm the validity of the clinical signs assigned to innocent murmurs; and this it has done.

TABLE I

DISTINCTIVE CLINICAL FEATURES IN 330 HEALTHY SUBJECTS WITH AN INNOCENT MURMUR

Special features	The murmur in mid-systole (262 cases)				The murmur in late systole (68 cases)
	The murmur of reclining posture (135)	The murmur of upright posture (80)	The loud variety of murmur (7)	The parasternal murmur (40)	
Age	Young subjects	Young adults	Young subjects	Older adults	Any age
Character	Blowing or roughish	Blowing or roughish	Blowing or roughish	Blowing or roughish	Blowing or roughish
Intensity	Not loud	Not loud	Loud	Loud	Loud
Effect of deep inspiration on intensity	Disappears to auscultation	Disappears to auscultation	Persists	Persists	Persists
Effect of posture on intensity	Louder in reclining posture	Louder in upright posture	Trivial	Trivial	Trivial
Effect of posture on distribution	Murmur appears in pulmonary area on reclining	None	Towards axilla in upright, and towards base in reclining posture	None	None

THE MURMUR OF RECLINING POSTURE

Among the clinical signs common to cases in whom a subsequent special examination showed no evidence of heart disease was the fact that the murmur was louder in the reclining than the upright posture. By itself such a sign cannot be distinctive, but along with others it eased the recognition of the murmur and this justified the name given to it. This group of innocent murmur held 135 of the 330 cases. Children under 10 were not accepted; 88 cases were between the ages of 10 and 19, 36 between 20 and 29, and 11 between 30 and 39; there was none older than 40 so that the murmur is confined to younger subjects. The murmur was never loud or long and because of this it was little conducted, and with few exceptions it was dispelled by deep inspiration. It was best heard over an area just internal to the mitral area. Tachycardia was without constant effect on its intensity. The murmur was always louder in the reclining posture, and it was characteristic of this group that as the subject reclined a murmur appeared in the pulmonary area. In 12 instances the pulmonary murmur was also audible in the upright posture, and, if so, the murmur was louder in the reclining posture at the pulmonary area than at the mitral. In 15 cases the pulmonary murmur added in the reclining posture was conducted towards the aortic area, but a silent area separated the pulmonary and mitral murmurs as in the other cases.

All 135 cases were referred for special cardiological examination because a diagnosis of valvular disease had been entertained, usually by more than one medical practitioner. In 38 there was a long history of cardiac invalidism on the grounds that the murmur indicated mitral disease. Twenty-five cases had suffered some time from rheumatic fever or chorea, and for that reason the murmur had gained a greater significance, and organic heart

disease was regarded as the cause with greater confidence. Among restrictions, handicaps, and penalties, to which subjects in this group had yielded, were rest in bed for several months, prevention from taking part in games and physical exercises including swimming, allocation to a low health category by Military Recruiting Boards denying admission for military service, dismissal from certain civilian occupations, and failure to enter others.

The Murmur of Upright Posture

This murmur was found in 80 of the total of 330 cases. Thirty-nine were between the ages of 10 and 19, 22 between 20 and 29, 16 between 30 and 39, and 3 between 40 and 43. A comparison of the age incidence of this group with the previous one shows that the murmur of reclining posture belongs to a rather earlier age than the murmur of upright posture, thus, for the former group the murmur was twice as common at ages under 20 years as over, and for the latter group it was twice as common at ages over 20 as under.

Unlike the murmur of reclining posture, this murmur was better heard in the upright posture. Although diffuse in its distribution over a small area internal to the mitral it was never conducted afar because it was never loud, and except for 13 instances it disappeared on deep inspiration.

All 80 subjects had been suspected by one or more medical practitioners of having mitral disease, and in 18 unwarranted invalidism had been enforced. As in the previous group so also in this one, such invalidism was commoner in the presence of a past history of rheumatic fever or chorea, and this applied to 13 cases.

The Loud Variety

Although only 7 examples of this murmur are cited it is likely that it is a good deal commoner than this figure suggests because the low incidence here is partly explained by the fact that its innocent nature was only recognized with certainty towards the end of this investi-

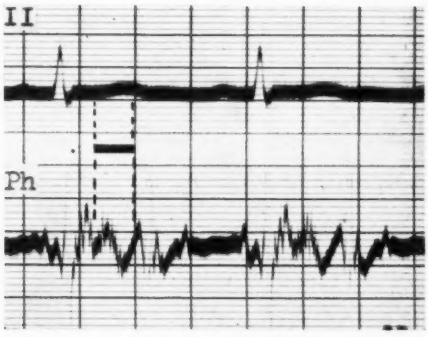

Fig. 6.—The loud variety of innocent systolic murmur.

gation; more cases have come to my notice since the present analysis was completed. Indeed the small number is not a measure of its importance for this lies in the certainty with which the murmur is mistaken for one indicating mitral disease. The ages ranged from 11 to 20 years so that this murmur, too, appears to be confined to young subjects.

The murmur was loud but never rough or harsh: like other varieties one of its peculiar features was its fineness, demonstrated by its roughish, blowing, or whiffy character. It was

lessened but never abolished by deep inspiration, and as in the case of other innocent murmurs, which were obscured or diminished by deep inspiration, it was noticed that when respiration was resumed the murmur regained its customary intensity only after two or three heart beats. It was diffuse in its distribution and in the cases examined it spread towards the axilla in the upright posture when it was loudest, and towards the sternal border and pulmonary area in the reclining posture.

On careful auscultation it was possible, unless hindered by tachycardia, to identify its position in mid-systole and the small gap between the first heart sound and the murmur, but a phonocardiogram was desirable to support the clinical diagnosis in this instance, for because of its intensity the murmur suggested the diagnosis of mitral disease; the phonocardiogram (Fig. 5 and 6) gave proof of its innocence by placing the murmur in mid-systole and by showing the absence of murmurs characteristic of mitral stenosis.

The Parasternal Murmur

This murmur was present in 40 of the 330 cases. Twelve were between the ages of 10 and 19, 9 between 20 and 29, 13 between 30 and 39, and there were 6 over 40.

Because the murmur was loud it was never abolished by deep inspiration. It was audible for a little distance away from its point of maximum intensity in the fourth intercostal space at the left border of the sternum. Posture had no great influence on its intensity. Although loud it was never harsh, and it was usually described as roughish, blowing, or whiffy, terms that emphasize the fineness of the vibration. The murmur was never associated with a thrill, which helped to distinguish it from the murmur of ventricular septal defect heard in the same position. Sometimes it was possible to make out on clinical auscultation that the murmur occupied mid-systole because of the short gap which separates the first heart sound from the murmur that follows it. This was told with certainty by the phonocardiogram (Fig. 7 and 9) which demonstrated the murmur starting a little distance beyond the S line and later than the murmur of ventricular septal defect which starts at the S line (Fig. 8 and 9).

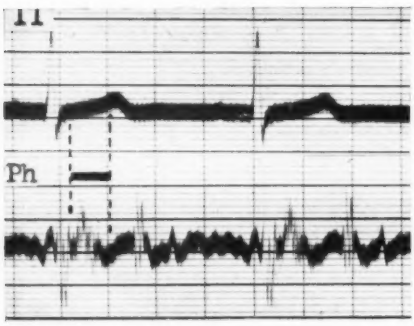

Fig. 7.—The innocent parasternal murmur.

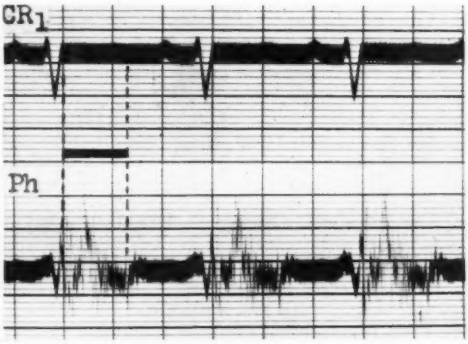

Fig. 8.—The murmur of ventricular septal defect.

The electrocardiogram was useful in this group of cases because it was always normal, whereas it was often abnormal in the cases of ventricular septal defect studied alongside the innocent group. In the same way cardioscopy was indispensable for there was never enlargement of the heart in the cases showing the innocent parasternal murmur, while in the patients with the congenital lesion there was often some degree of right heart enlargement.

Owing to the peculiar site of the murmur most of these cases had been regarded as instances of congenital heart disease, but some had been diagnosed as mitral disease, especially those with a past history of rheumatic fever, 10 in number.

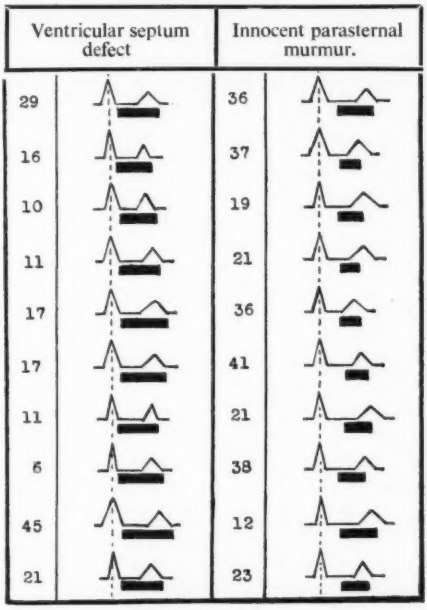

FIG. 9.—Position of murmurs in relation to the electrocardiogram in 10 patients with ventricular septal defect, and in 10 subjects with innocent parasternal murmur. Numerals denote ages.

THE MURMUR IN LATE SYSTOLE

In this important group there were 68 cases. Seventeen were between the ages of 10 and 19, 12 between 20 and 29, 15 between 30 and 39, 13 between 40 and 49, and 6 between 50 and 59; there were 5 over 60 years of age.

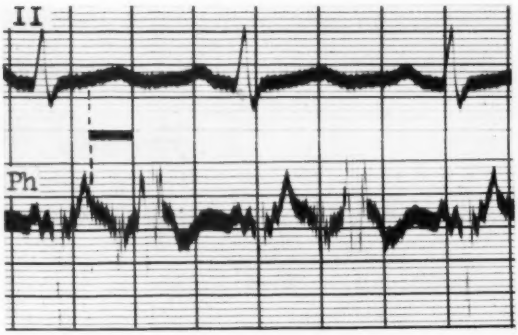

FIG. 10.—The innocent murmur in late systole.

FIG. 11.—The innocent murmur in late systole.

The murmur was loud and for this reason it was heard some distance away from its site of maximum intensity in the mitral area, and it was still audible on deep inspiration. Posture had no specific effect on the murmur although in many it was a little louder in the upright posture. The quality of the murmur was never rough or harsh, and in common with other innocent murmurs it was described as roughish or blowing. Its most distinctive feature was its lateness in systole for it was placed nearer to the second than the first heart sound showing an obvious gap between the first sound and the murmur. The phonocardiogram (Fig. 5, 10, and 11) always confirmed its position towards the end of systole; it started near the commencement of the T wave and seldom lasted till the end of systole and the second heart sound. In other cases, not included here, a clear *sound* appeared in late systole initiating an innocent kind of triple heart rhythm.

As the murmur was so loud and as it occurred in subjects of all ages, it proved even a greater source of unwarranted invalidism, for once consigned to this inferior health category it lasted for a lifetime because the murmur lasted as long.

Summary: Innocent Murmurs

The common incidence of innocent murmurs and the unwarranted cardiac invalidism resulting from it give to the problem of distinguishing them from murmurs arising from heart disease a priority unequalled by any other in clinical cardiology. There is urgent need to set a clinical and cardiographic pattern for this murmur, which will make it easy to recognize. The fact that there is as yet no clue to the mechanism of its production need not promote theoretical speculation as to its cause for that might hinder rather than help in its diagnosis. From a study of 330 healthy subjects presenting a murmur, it became possible on clinical grounds alone to recognize its innocent character by placing the cases in five groups (see Table I) which have been named according to the main clinical feature. Thus, the murmur of *reclining posture* was roughish or blowing in character and was confined to young subjects; it was uncommon after 30 and absent after 40 years of age. The murmur was not loud and for that reason it was often removed by deep inspiration. It was loudest in the reclining posture, and with this posture a murmur developed in the pulmonary area. Sometimes this last murmur was audible in the upright posture too, and in this circumstance in the reclining posture it was louder in the pulmonary than mitral area. The murmur of *upright posture* was also confined to younger subjects and the oldest case was 43. It was roughish or blowing in character and was best heard in the upright posture. A *loud* variety of innocent murmur was less common, but its loudness invariably caused it to be mistaken for the systolic murmur of mitral disease: hence its importance. It occurred in young subjects. Change of posture affected the distribution of the murmur more than its intensity, so that in the upright posture it became louder towards the axilla, and in the reclining posture upwards and towards the sternum. The *parasternal* murmur was loud and was best heard in the fourth intercostal space near the left border of the sternum, but it was never accompanied by a thrill as the murmur belonging to ventricular septal defect usually is. The murmur in *late systole* was loud and was roughish in character. It occurred at all ages. It could be told easily by clinical auscultation for the murmur was placed nearer to the second than the first heart sound.

The phonocardiogram confirmed the validity of this clinical classification. In the first four varieties the murmur was recorded in mid-systole, and in the last variety in late systole. In none did the tracing show a diastolic murmur.

II. THE MURMURS OF MITRAL VALVE DISEASE

The diagnosis of long standing mitral stenosis presents no difficulty as a rule for it produces obvious physical signs. When the lesion is early its recognition may prove difficult,

while the addition of hypertension and/or of auricular fibrillation, especially when the heart is rapid, may confound the diagnosis. Great help in giving to certain auscultatory signs their true significance has come from radiology; even the presence of unusual physical signs may not prevent diagnosis of the valvular lesion after taking stock of the size and shape of the heart at cardioscopy. None the less, since the left auricle impresses the œsophagus in health, the slight departure from the normal found in early distension of the left auricle in mitral disease, often leaves a difficulty in the radiological interpretation. Two other circumstances obstruct the radiological diagnosis of mitral stenosis; first, in rare instances of undoubted mitral stenosis the heart at cardioscopy is unaltered in shape and size; secondly, when the left ventricle is enlarged from hypertension or aortic valvular disease, it deepens the left auricle impression in the right oblique view in much the same way as does the distended left auricle of mitral stenosis, although help in the differentiation can come from examination in the left oblique view. These difficulties compel a critical re-examination of the auscultatory signs of mitral disease and an inquiry into the graphic registration of those murmurs made familiar by auscultation. The three murmurs associated with mitral disease will now be considered separately.

The Presystolic Murmur

A phonocardiogram was recorded in 33 patients with mitral stenosis who showed the characteristic presystolic murmur on auscultation. The association of a murmur and a loud first sound had produced a rough note which might be represented as *thurr-rupp*; this was

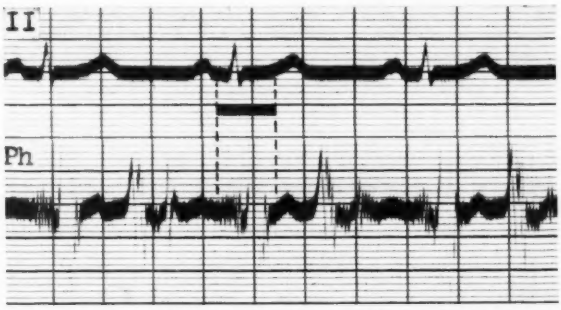

Fig. 12.—Auricular murmur in mitral stenosis where auscultation showed a presystolic murmur.

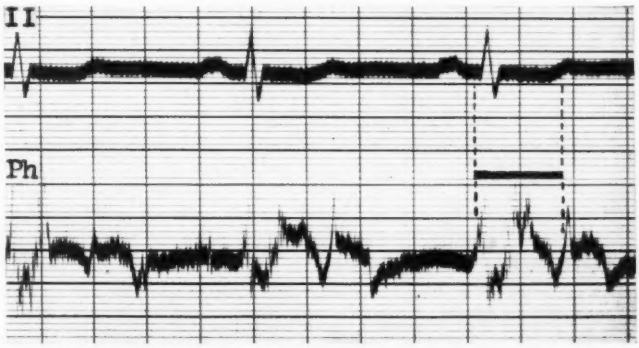

Fig. 13.—Auricular murmur in mitral stenosis where auscultation showed a presystolic murmur.

louder and more abrupt than splitting of the first heart sound found in healthy subjects, which might be represented as *r-rupp*. Although a crescendo character is customarily described for the presystolic murmur, such an effect is an auditory impression gained during auscultation for graphically the murmur does not show such progressive intensification.

In 31 cases the murmur started during the P–R period of the electrocardiogram (Fig. 5); it started at the end of the P wave in 14 (Fig. 12), early in the P–R period in 8, and late in 9 (Fig. 13). In the light of this graphic representation the term presystolic may be used as by this is meant pre-ventricular-systole, but since the murmur takes place during systole of the auricle, the term *auricular systolic murmur* is more informative, and is the name that best conforms to its scientific interpretation. In only 2 cases did the murmur, which clinically was indistinguishable from the one heard in the other 31 patients, fail to show earlier than the S line, this marking the early phase of ventricular contraction. In both it was noticed that the P wave showed a small voltage, its amplitude being less than one millimetre.

In 19 cases a mid-diastolic murmur was continued into the period of auricular systole and joined with the auricular murmur, while in the remaining 14 patients the diastolic murmur had almost spent itself before the auricular systolic murmur started.

Occasionally the friction sound in acute pericarditis (Fig. 14) can simulate the auricular

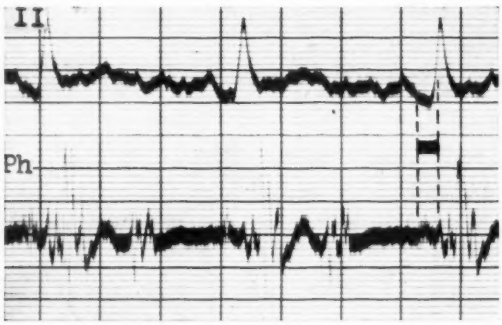

FIG. 14.—Friction sound during auricular systole in acute pericarditis.

murmur of mitral stenosis, but is easily distinguished on clinical grounds—its disappearance in a few days, the absence of a mid-diastolic murmur, and the history of the illness.

THE SYSTOLIC MURMUR

A phonocardiogram was recorded in 41 patients with undoubted mitral stenosis in whom a mitral systolic was heard on auscultation, but a presystolic murmur could not be elicited although it was sought in each case after inducing tachycardia.

In 33 the murmur commenced during the P–R period of the electrocardiogram (Fig. 5); in 8 it started at the end of the P wave (Fig. 15); in 11 early in the P–R period; in 14, late (Fig. 16). Such findings are surprising for they are the same as those in the series of patients with mitral stenosis showing a presystolic murmur. There were 8 cases in which the murmur commenced at the S line marking the early part of ventricular contraction (Fig. 17); in each of these cases a mid-diastolic murmur was present. In common with the two similar cases in the presystolic murmur series, they showed a small voltage of the P wave in the electrocardiogram with an amplitude less than one millimetre.

In 13 cases a mid-diastolic murmur was continued into the period of auricular systole and joined with the auricular murmur, while in the remaining 28 patients the diastolic murmur had almost spent itself before the start of auricular systole.

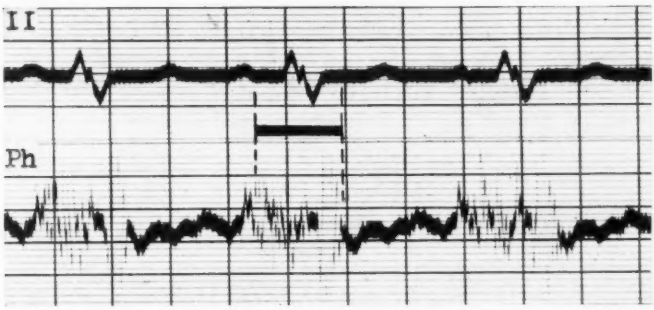

FIG. 15.—Auricular murmur in mitral stenosis where auscultation showed a systolic murmur.

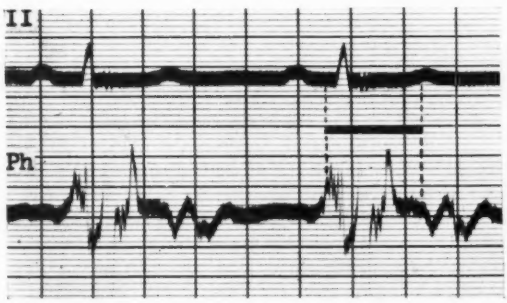

FIG. 16.—Auricular murmur in mitral stenosis where auscultation showed a systolic murmur.

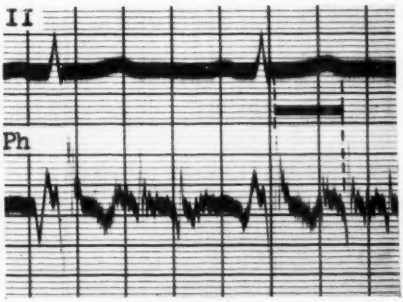

FIG. 17.—A murmur in mitral stenosis where auscultation showed a systolic murmur, which commences at the S line. Confirmation of mitral stenosis is found in the mid-diastolic murmur following the third heart sound.

THE MID-DIASTOLIC MURMUR

A further significant finding in this investigation has been the invariable presence in the phonocardiogram of a mid-diastolic murmur: it was present in every one of the 74 cases, 33 of which had a presystolic murmur and 41 a systolic murmur on auscultation. The murmur was attached to the end of the third heart sound, and in 32 cases it was continued into the period of auricular systole and was joined to the auricular systolic murmur (Fig. 18), while in the remaining 42 patients the diastolic murmur had almost disappeared when the auricular murmur started.

On clinical auscultation the mid-diastolic murmur was not elicited in 11 patients, and in 12 others the added sound was thought to be the third heart sound devoid of a murmur. The murmur was heard in the remaining 51 patients, but in 21 of these it was necessary to

listen towards the axilla with the patient inclined on the left side after induced tachycardia. In many cases with a rapid heart rate, however, the mid-diastolic murmur found on auscultation appeared to be contiguous with the auricular systolic murmur following closely on it.

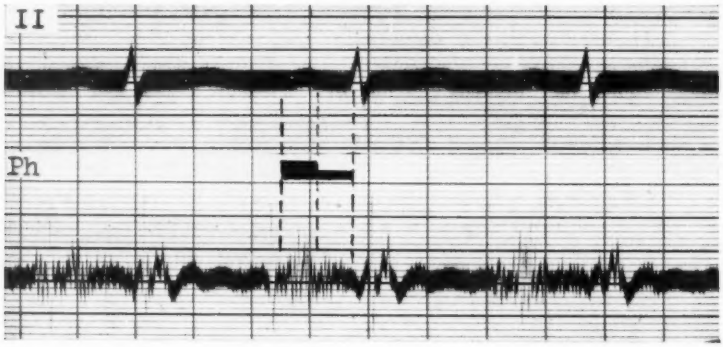

FIG. 18 —The mid-diastolic murmur of mitral stenosis, which is contiguous with the auricular murmur.

AURICULAR FIBRILLATION IN MITRAL DISEASE

Naturally, in auricular fibrillation the auricular systolic murmur was absent although often the mid-diastolic murmur approaching the ventricular part of the first heart sound provided a clinical impression of a presystolic murmur.

A phonocardiogram was taken in 20 patients with mitral stenosis and auricular fibrillation; in each the systolic murmur started at the S line, i.e. at the onset of ventricular contraction (Fig. 19). This was unlike auricular fibrillation in other conditions showing a systolic murmur such as hypertension where the murmur started later and in mid-systole (Fig. 20). Phono-

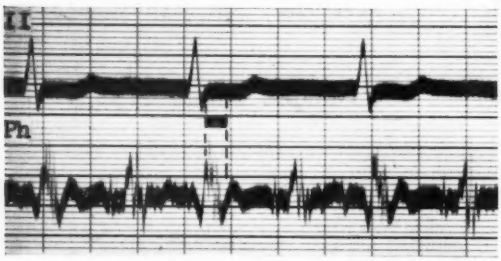

FIG. 19.—The systolic murmur in mitral stenosis with auricular fibrillation, which starts at the S line.

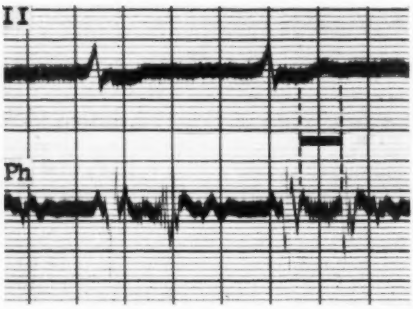

FIG. 20.—The systolic murmur in hypertension with auricular fibrillation, which starts in mid-systole and some way after the S line.

cardiographically, therefore, the diagnosis of mitral disease as the cause of fibrillation is assisted by a regard of the place of the systolic murmur; confirmation comes from finding a mid-diastolic murmur in every case. During a long diastolic phase this murmur was isolated in mid-diastole, but with a shorter diastolic period the murmur was continued up to the ventricular part of the first heart sound of the next beat.

SUMMARY: MURMURS OF MITRAL DISEASE

With two exceptions in 33 patients with mitral stenosis who had a presystolic murmur, the phonocardiogram showed the murmur starting within the P–R period, that is, during auricular systole; in the two exceptions where the murmur started at the S line marking the early phase of ventricular contraction, it was noticed that the P wave of the electrocardiogram was less than one millimetre in amplitude.

The most significant finding in this investigation is that in patients with mitral stenosis where a systolic murmur was heard on auscultation and a presystolic murmur was not elicited even after inducing tachycardia, the murmur also started during the P–R period in the majority (33 out of 41). Thus, the systolic murmur of mitral disease, like the presystolic murmur, was produced by auricular systole in such cases. The conditions in the 8 exceptions tallied with those found in the two similar examples in the presystolic murmur series, in that the murmur started at the S line, and was associated with a small P wave (of less than one millimetre in amplitude).

These graphic findings endorse the specific role of auricular contraction in producing the systolic as well as the presystolic murmur and support the view that a diagnosis of mitral stenosis should be applied to mitral valve disease whichever of the two murmurs it presents on clinical auscultation. Even in the 10 cases (2 with presystolic and 8 with systolic murmur on auscultation) where the murmur in the phonocardiogram was seen no earlier than the S line the application of the term " mitral incompetence or regurgitation " would be inaccurate because in each of them there was a mid-diastolic murmur to give proof of mitral stenosis. Indeed a mid-diastolic murmur was present in the phonocardiogram in each of the 74 cases of mitral disease, whether with a presystolic or systolic murmur, emphasizing on the one hand its value in a case with equivocal clinical and radiological signs, and on the other hand the need of searching diligently for this murmur under the most favourable circumstances, namely to listen attentively after inducing tachycardia and inclining the recumbent patient to the left side. A detailed analysis of the phonocardiograms from the two series of patients failed to explain what determined in mitral stenosis whether the murmur should be of the presystolic or systolic kind. It neither depended on the length of the P–R period nor on the duration of the diastolic phase, nor was the graphic registration of the murmur distinctive for each group. It can only be surmised that the intensity and abruptness of the first heart sound decides the presence or absence of the rough quality that typifies the presystolic murmur.

PHONOCARDIOGRAMS OF AURICULAR MURMURS
FROM A CASE WITH MITRAL STENOSIS AND HEART BLOCK

BY

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It is well known that an auricular sound can sometimes be recognized by means of the stethoscope or phonocardiogram. In some instances it can be shown that the so-called first heart sound consists of a fusion of an auricular sound with a ventricular sound, and this may be evident in cases with prolongation of the P–R interval. This, however, is generally not easily recognized; otherwise there should be a presystolic sound or a double first heart sound in all cases of partial A–V block.

In their monograph, Orias and Braun-Menendez (1939) state that three different acoustic phenomena contribute to the auricular first heart sound, namely—and in the following order—vibrations in the contracting auricles, the dilatation of the ventricles during their filling with blood, and vibrations in the mitral and tricuspid valves at the closure of the corresponding orifices at the end of the auricular systole. The first mentioned can only be studied from the œsophagus; the other two from the præcordium also.

It is stressed by different authors (Orias and Braun-Menendez, 1939; Bramwell, 1935; and Cossio and Fongi, 1936) that the auricular first heart sound will be increased during conditions, when the blood stream through the auriculo-ventricular orifices is increased or hastened (thyrotoxicosis, hypertension, and mitral stenosis with left auricular hypertrophy). It is also easy to understand that the rigidity of the valves in mitral stenosis might change the auricular sound to a murmur. If the statement of Levine (1941) is true, that seven-eighths of the blood stream from auricles to ventricles passes the orifice only on account of pressure-equalization, whereas the last eighth is caused by auricular contraction, it will be clear that only the presystolic murmur in mitral stenosis is caused by auricular systole. This is also evident from the fact that the presystolic part of the diastolic murmur disappears when auricular fibrillation starts and there is no regular auricular systole.

We have recently studied a case of mitral stenosis with complete heart block, where the auricular murmur is very beautifully demonstrated on the phonocardiogram. As such cases are rare, according to Lewis (1944), and also from our own experiences, it might be of interest to report one instance. The physical and phonocardiographic quality of the sound places it in the class of *murmurs*.

Case Report

A woman, 49 years old, whose mother and grandfather and uncle had organic heart disease, had diphtheria in childhood and acute rheumatic fever at the age of 18. At the age of 25 dyspnœa and irregular heart action developed and the diagnosis of organic heart disease was made. She had a second attack of rheumatic fever four years later, after which there was increasing breathlessness, nocturia, pain in the chest, and irregular heart action.

The examination at the Sabbatsberg's hospital in 1943 revealed slight pre-tibial œdema and

dyspnœa on action. Over the whole heart systolic and diastolic murmurs with their maxima over the heart base were heard. The rhythm seemed to be regular with some few premature beats. The blood pressure was 175/110. X-ray of the heart was normal, the size being 415 c.c. per square metre body surface. The cardiogram revealed a partial A-V block, which could not be influenced by atropine, alternating with complete heart block. The degree of the block seemed to be related to the course of the subjective symptoms.

At a fresh examination in 1945 there was, besides the above-mentioned murmurs, a peculiar, changing, possibly presystolic murmur over the apex, which made the occurrence of an auricular murmur suggestive. There was now complete heart block and right axis deviation in the cardiogram, as compared with normal axis in 1943.

Phonocardiograms (Fig. 1) confirmed this origin of the new murmur. In all frequencies—especially the lower ones—there was besides the harsh systolic murmur over the apex, a murmur that was constantly related to the auricular activity (P wave). When the auricular systole appeared on its " normal " place in the chain of events, the auricular murmurs caused a typical presystolic murmur. Otherwise it was atypically located in the heart cycle. When

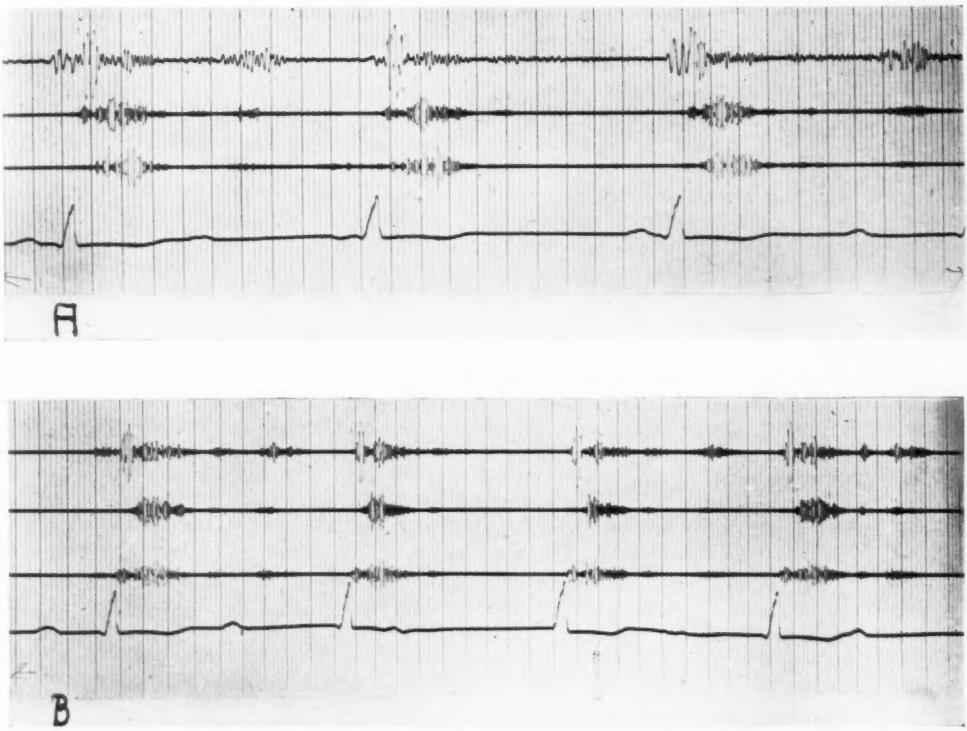

FIG. 1.—Calibrated phonocardiograms of the case described. (A) The upper three lines show the phonocardiograms with frequencies 15–100, 170–290, and 400–850 cycles, and the lowest line the electrocardiogram. (B) The upper three lines show the phonocardiograms with frequencies 80–180, 260–520, and 15–850 cycles, and the lowest line the electrocardiogram. In each instance the auricular contraction (P wave) is accompanied by the specific auricular murmur, independent of any relationship to the ventricular activity.

C

it occurred independently it was evident that the murmur was not of the crescendo type, as has often been alleged. This is, as White (1944) has pointed out, an illusion caused by the close relationship between the presystolic murmur and the first heart sound, in which it is finally absorbed. In the case presented the auricular murmur was recorded on the phonocardiogram 0·16 sec. after the beginning of the P wave, which approximately corresponds to the findings of Orias and Braun-Menendez (1939). The duration was 0·14–0·16 seconds.

Summary

A case of rheumatic heart disease with aortic stenosis and regurgitation and mitral stenosis is reported, where the existence of a complete heart block clearly demonstrates the auricular origin of the presystolic murmur in mitral stenosis.

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CHRONIC AURICULAR TACHYCARDIA

BY

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There are exceptions to all the criteria employed for the differentiation of paroxysmal auricular tachycardia from other forms of rapid heart action. Nevertheless, the three most constant features are the sudden onset, the short duration (rarely more than ten days), and the sudden termination. We have had the opportunity of observing a case, which while falling into the category of paroxysmal tachycardia, yet differed from the classic type in its chronicity and in its response to treatment.

Case History. A man, aged 31, was admitted to Southmead Hospital on May 27, 1946, with persistent tachycardia. There was no past history of scarlet fever, rheumatism, or diphtheria. A paternal uncle gave a history of bouts of tachycardia since adolescence, lasting anything from minutes to two days.

He was taken prisoner by the Japanese in Bandoeng, Java, on March 8, 1942. As a prisoner he was made to work hard and given poor rations. During 1942 his diet consisted of 400–500 g. of rice daily, a variable quantity of local green vegetables, and an occasional small ration of meat. Later the rice was cut down to about 100 g. a day and was supplemented by an addition of tapioca bread; meat practically disappeared from the diet. During his captivity he had three attacks of bacillary dysentery and dengue once. In 1942, cases of nutritional neuropathy began to occur and were seen in ever-increasing numbers. He escaped with only slight numbness down both shins, starting two months before release. In September 1945 he was repatriated and had an adequate diet.

During the early part of 1944 he began to get attacks in which he was conscious of his heart beating rapidly and apparently regularly. These attacks lasted about half an hour, and occurred very irregularly. The initial ones stopped spontaneously, and later he learnt to control them by taking a deep breath, leaning forward, and sometimes breaking wind. His medical attendant stopped one attack by carotid pressure.

After he had been subject to these attacks for about six months he found that they persisted longer and were more difficult to terminate. On the ship that brought him back from Singapore in October 1945, some lasted thirty-six hours.

On December 11, 1945, he started an attack of tachycardia, and this was noted by a member of a medical board which discharged him from the Services. He stated that this condition had persisted without interruption ever since. In February 1946 he complained of troublesome dyspnœa on exertion, and this increased rapidly thereafter. His ankles did not swell, and he had no præcordial pain. During the first week in May his doctor sent him for an X-ray, and cardiac enlargement was found, together with pulmonary congestion. He was ordered to bed and given 15 mg. of vitamin B_1 daily for two weeks with no apparent effect, and subsequently admitted to hospital.

Examination. He was found to be well covered, and was not nervous or distressed. There was no cyanosis of the cheeks or mucous membranes. Dyspnœa occurred on slight exertion but not on lying down. No focal infection was found in the teeth or throat. There

was no thyroid enlargement, no tremor of the outstretched hands, nor was his skin unduly moist. No abnormality was found on examination of the central nervous system.

The cervical veins were distended, and the liver was enlarged two fingers' breadth below the costal margin. No signs of pulmonary congestion or effusion into serious cavities were found, and there was no œdema. The apex beat was in the sixth intercostal space in the anterior axillary line. No thrills were felt. The heart was beating regularly at the rate of 168 a minute (Fig. 1); the sounds were normal and there were no murmurs. The blood pressure was 105 systolic and 70 diastolic, and showed no postural alteration. Carotid

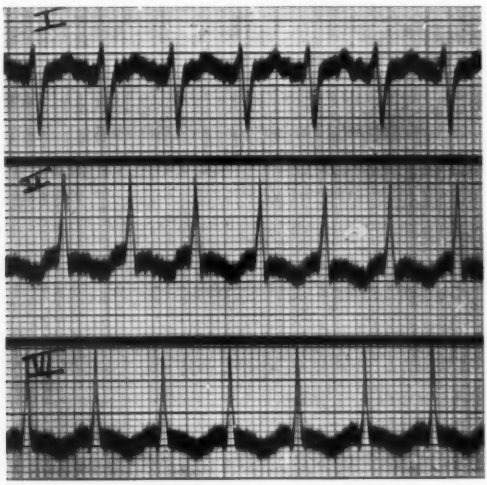

FIG. 1.—Initial cardiogram, May 28, 1946. The three standard leads are shown. The rate is 168 a minute and is regular. T is upright in lead I and inverted in leads II and III.

and eyeball pressure had no effect on the tachycardia, nor was there any alteration with changes of posture, exercise, or phases of respiration.

A teleradiogram showed generalized cardiac enlargement and pulmonary congestion. The hæmoglobin was 108 per cent, the red blood count 5,300,000, and the white blood count 10,200. The Wassermann reaction was negative. No abnormality was found on examination of the urine. The cardiographic findings, on which a diagnosis of paroxysmal tachycardia was made, will be analysed in a later section.

Progress. Quinidine therapy was attempted and abandoned because he was hypersensitive to small doses.

On June 12 he was given 9 grains of digitalis, and this dosage was continued daily for eleven days, after which it was reduced to 6 grains. On these large doses of digitalis the pulse rate fell during sleep and also showed a gradual decline during the waking hours. On the 27th he complained of nausea and vomiting, and his pulse fell to 80. Digitalis was discontinued. At this time vagal effects were easily induced. Lying on his left side caused bradycardia, and occasionally even cardiac standstill; both Valsalva's experiment and carotid sinus pressure had the same effect.

On July 4 a cardiogram showed that the rhythm had returned to normal, and his pulse rate was 75 a minute. The cervical veins were no longer distended, and the liver was not

palpable. A teleradiogram showed that the transverse diameter of the heart was 4 cm. less than on admission.

There was a gradual acceleration of the pulse over the next four days to 150 a minute, with a return of the abnormal rhythm in the cardiogram. Because of the fall of the pulse rate during sleep while on digitalis, it was decided to try and assess the effect of the higher centres in the production of the tachycardia. He was anæsthetized with a small intravenous dose of pentothal, but there was no fall in the pulse rate.

On July 12 he was given 0·5 mg. of prostigmine intramuscularly. Fifteen minutes later carotid sinus pressure restored normal rhythm, which persisted only for five minutes. The following day 1 mg. of prostigmine was injected and with the help of carotid pressure a short period of cardiac standstill occurred. The ectopic rhythm returned almost at once. Within half an hour toxic effects, in the form of sweating and muscular twitchings, were noted. On the 14th, ½ mg. tablets of prostigmine were given three times daily, and on this dosage his pulse tended to remain about 130 a minute. In order to augment the effect of the prostigmine 5 g. each of potassium chloride and potassium citrate were given with every dose. This caused severe epigastric pain, sweating, and inability to speak. The dose of potassium salts was reduced by half and this was well tolerated, but appeared to be without effect on the pulse rate, and was, therefore, discontinued.

On July 28 he was started on 1 grain of digitalis, four-hourly, in addition to the prostigmine. By August 7 he complained of diarrhœa, so the dose of digitalis was reduced to three times a day. There followed a period during which the heart rhythm and rate were unstable. Short periods of cardiac standstill were followed by a series of normal beats or by an almost immediate return to the ectopic rhythm. Furthermore, it was found that when he was supine his pulse dropped to 83; the rhythm was of sinus origin. On sitting up or standing the ectopic rhythm generally returned and the pulse rose to 120. These postural effects were gradually lost over the next ten days as the pulse rate slowed to 80 and the rhythm reverted to normal. All treatment was discontinued on August 16. The arrhythmia recurred, and by August 24 the pulse had risen to 160 a minute.

Cardiographic Analysis

Numerous cardiograms were taken during the period of observation. In the initial curve on May 28, 1946 (Fig. 1) the rate was 168, and there was right axis deviation. It was interpreted as showing paroxysmal tachycardia, although at this stage the possibility of flutter had not been excluded.

On June 21, ten days after starting digitalis, the cardiogram had appreciably altered (Fig. 2). The rate was 145. An inverted P could be seen in all three leads with a P–R interval of 0·16 sec. T wave was upright in lead I and inverted in leads II and III. Inversion of T in leads II and III is well recognized in paroxysmal tachycardia of long duration (Campbell, 1942).

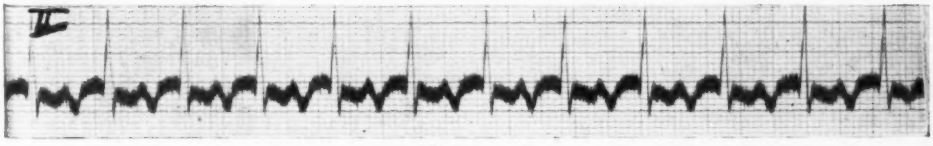

Fig. 2.—Lead II, June 21. The P–R interval is 0·16 sec. The P wave is large and inverted. T is also inverted. This and subsequent cardiograms have been reduced to nine-tenths.

On June 24 it was found that getting the patient to lie on his left side caused the pulse to become irregular, and even induced sinus block. This is shown in lead II of Fig. 3, in which there is a ventricular extrasystole followed by a normal complex with upright P, and then an ectopic P wave (P1), which failed to excite a ventricular contraction because the conducting tissue was in a refractory state. After 1·2 sec. a normal beat followed, and then 0·8 sec. later there was another normal beat, the T wave of which was succeeded 0·08 sec. later by a series of ectopic beats. In the first of these the P–R interval was 0·28 sec., and in the next

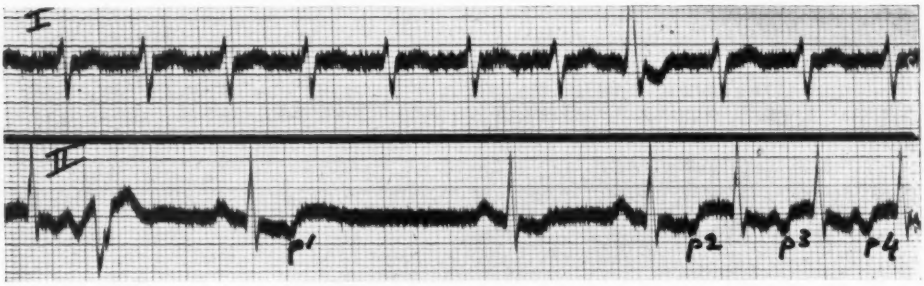

FIG. 3.—Leads I and II, June 24. Lead II shows the effect of lying on the left side while on large doses of digitalis.

0·2 sec. It was considered that the prolongation of the P–R interval to 0·28 sec. resulted from the premature ectopic impulse reaching the A-V junctional tissue so early that it found it in a relative refractory phase. The distance between P3 and P4 in Fig. 3 is 0·48 sec., and the distance between P1 and P2 is 2·4 sec., which is five times 0·48 sec. This suggests a parasystolic ectopic rhythm of rate 125 a minute. In lead I there was a ventricular extrasystole that did not alter the fundamental rhythm. With continuance of digitalis the P–R interval increased steadily and by June 26 it was 0·24 sec.

On June 28 (when digitalis had been discontinued because of the toxic effects it had produced) a curve was obtained (Fig. 4) which demonstrated increased sensitivity to vagal influence. Lead II showed the end of a long period of sinus block produced by Valsalva's experiment, followed by normal beats with inverted T waves. The shape of the T wave in this, as in other curves, was doubtless influenced by the digitalis which had been administered.

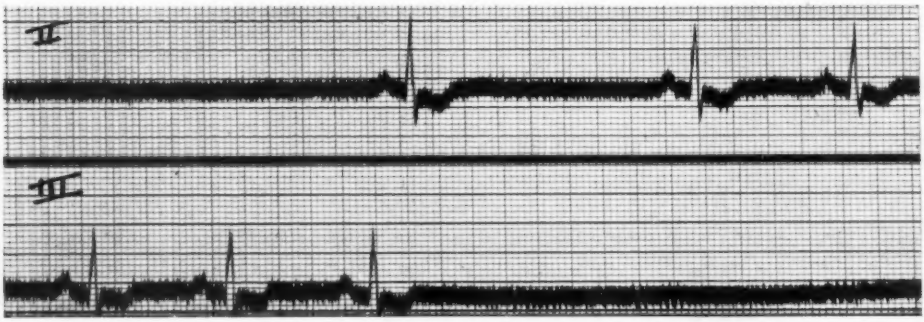

FIG. 4.—Leads II and III, June 28. Lead II shows the effect of Valsalva's experiment. Lead III shows the effect of bilateral carotid sinus pressure.

Lead III showed the start of another long period of sinus block due to carotid sinus pressure.

The effects of 0·5 mg. of prostigmine given on July 18 are seen in Fig. 5. All these curves were taken on lead II. The first one was obtained before the injection, the second after ten minutes, and the third after a further five minutes during bilateral carotid sinus pressure.

FIG. 5.—July 18. All curves are lead II. The top curve was taken before prostigmine 0·5 mg. intramuscularly; the middle, ten minutes after, and the lower with bilateral carotid sinus pressure.

Fig. 6 was obtained on July 4, and shows cessation of the paroxysmal tachycardia. The rate was 75 a minute, and the P–R interval was 0·16 sec. P was upright in all three leads, and T was inverted in leads II and III.

The præcordial lead CRI was used to study auricular activity. In Fig. 7 the first complex is normal and is followed by an ectopic P which is blocked. There follows, after a pause,

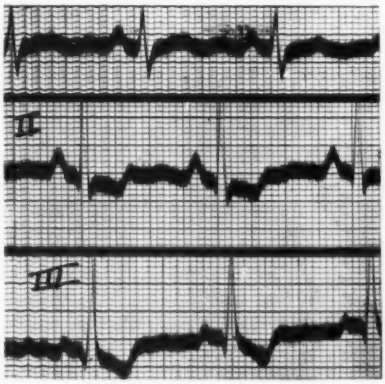

FIG. 6.—Leads I, II, and III, July 4, showing normal rhythm at the rate of 75 beats a minute. The P waves are upright, and T is inverted in leads II and III.

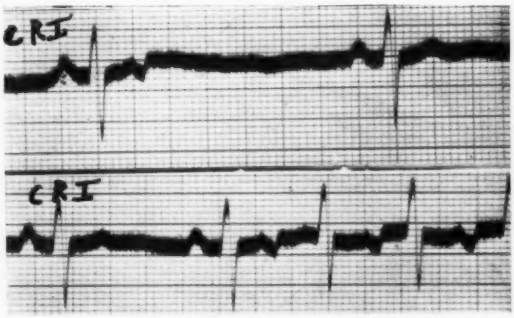

FIG. 7.—Præcordial lead CR_1. A blocked ectopic P is clearly shown in the first curve. The change-over from normal to ectopic rhythm can be seen in the lower curve.

one further normal complex. In the second curve a series of ectopic beats are shown after a normal complex. In neither of these two cardiograms, nor in others, is there evidence of an A-V block.

On August 15 (eighteen days after starting combined prostigmine and digitalis therapy) three cardiograms, each on lead II were taken shortly after 15 mg. of prostigmine had been taken by mouth (Fig. 8). In (A) the patient was lying down; a blocked ectopic P (P1) followed the first normal complex, and there followed a long compensatory pause, after which the ventricles responded to an impulse originating in the sino-auricular node. Then followed

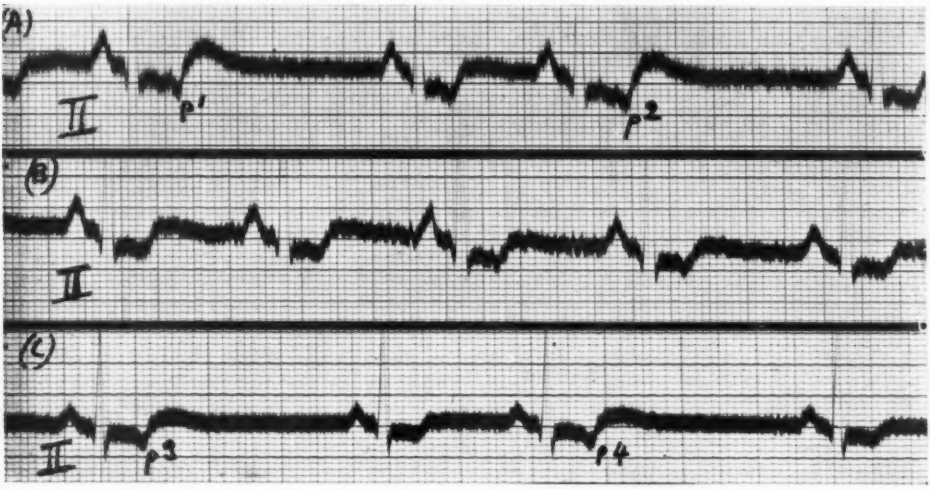

FIG. 8.—August 15. All curves are lead II. (A) was taken lying down; (B) sitting up, and (C) sitting up during bilateral carotid sinus pressure. The curves were taken ten minutes after a 15 mg. tablet of prostigmine had been taken by mouth.
(A) and (C) show an ectopic P wave following every second normal complex.

yet another normal beat, and then a second ectopic P (P2) bearing the same relation as P1 to its preceding QRS. The effect of this grouping was to produce pulsus bigeminus. In (B) the patient was sitting up: the rate was 60 and regular, and the P–R interval was 0·16 sec.; P was upright and T inverted. (C) was taken whilst the patient was sitting up, during carotid sinus pressure, and was very similar to (A). This showed that recumbency had an effect on the heart in this case equivalent to direct carotid pressure. The intervals P1, P2, and P3, P4 in Fig. 8 are the same as P1, P2 in Fig. 3 obtained fifty-two days earlier. This finding favours the interpretation of the tachycardia in terms of parasystolic ectopic rhythm.

In the cardiogram ectopic P waves, when following normal complexes, show a fixed relation to them, merging with the preceding T, and occur at a time when the junctional tissue is in a relative refractory state. Whether the impulse reaches the ventricle will depend upon the degree of vagal tone. If this is high it will further depress the conductivity and block the impulse.

Discussion

Sinus tachycardia can be excluded on the cardiographic evidence of ectopic P waves. The progressive lengthening of the P–R interval produced by large doses of digitalis and also the effects of vagal stimulation during therapy with digitalis or prostigmine do not suggest auricular flutter. Evans (1944) has stressed the importance of the chest lead CR_1 for the study of auricular activity. He is of the opinion that by this means a 2 : 1 A-V block can always be uncovered in paroxysmal tachycardia and that the difference between this condition and flutter is merely the rate of auricular contractions. Campbell (1945) was unable to confirm Evans's findings, as he could exclude an A-V block in at least thirteen of his own sixty-six cases. He considers that the shape of the auricular curves and the presence of an iso-electric level rule out flutter, even if a block can be demonstrated. We could not find an A-V block in any of our tracings in spite of the use of præcordial leads.

The chronicity of the tachycardia and the effects of treatment make this case exceptional. Digitalis produced first a tendency for the pulse to drop during sleep, and then a gradual slowing of the cardiac rate. At one stage, a combination of digitalis and prostigmine made the pulse rate susceptible to change of posture. Each time therapy has been discontinued the arrhythmia has recurred. Classification of this case is especially difficult, because a combination of all these features has seldom been recorded.

Wilson and Hermann's (1923) patient, in whom tachycardia had persisted for fifteen months at the time he was first seen, appeared to be strikingly similar to ours, but refused further treatment before a final result could be obtained; there were similar periods of bradycardia and standstill after digitalization. Maddox (1937) recorded an example of paroxysmal tachycardia lasting at least sixty-nine days in which the attack terminated gradually without the help of digitalis. In his case the pulse slowed spontaneously during sleep. Rest in recumbency for half an hour or more had a similar effect, inducing a 3 : 1 block with a pulse rate of 56, and a conduction time of 0·2 sec. With exercise the pulse rose suddenly to 168 while the conduction time remained 0·2 sec. He did not specifically investigate the effects of posture on the cardiogram. Attempts to restore normal rhythm with quinidine, digitalis, acetylcholine, adrenaline, and atropine, were unsuccessful. Because of the change of pulse rate with exercise and rest he considered that the extracardiac nerves were mainly responsible. This is of interest in view of the exposure of our patient whilst a prisoner to conditions favouring the production of nutritional neuropathy.

Miller and Perelman (1945) reported two cases of chronic auricular tachycardia, both with aberrant P waves, which showed striking changes of rate with posture, the rate being slower lying than standing. In their first case posture not only changed the rate but also the direction of the P wave in lead I. Digitalis abolished the orthostatic acceleration of the pulse rate. In their second case, digitalis did not control the tachycardia and there was no response to quinidine or to potassium salts. This experience led them to recommend that cardiograms should be taken in three positions, standing, sitting, and lying. The importance of this is further emphasized by the reports by Manning and Stewart (1945), and by Holmes and Weill (1945) of the finding of a prolonged P–R interval in healthy young adults, with a decrease to normal on standing. Our case resembles those of Miller and Perelman in its chronicity; the arrhythmia has been present for seven months, and can only be satisfactorily controlled by full doses of digitalis and prostigmine. However, orthostatic phenomena were not present on admission, and were only obtained for short periods just before full therapeutic effect was reached.

The continuous activity of a parasystolic auricular focus with a low degree of exit block under partial control of the extrinsic cardiac nerves, was postulated, though without proof, by Miller and Perelman to explain their findings. Only when it can be shown that the

intervals between premature systoles from a common focus are equal, or are multiples of a common denominator, and occur without fixed relationship to the beats of sinus origin, can parasystole be diagnosed with confidence. In our case we have been able to show that periods between ectopic beats from a single focus have a common denominator, but the fixed relation of the ectopic beats to beats of sinus origin which can be seen in the cardiograms is a serious obstacle to the acceptance of parasystole. The fixed relationship to the preceding beat may be explained by the theory of re-entry, but Scherf (1929) has produced evidence to show that these extrasystoles are released from an ectopic centre by the preceding normal beat.

Summary

An unusual case of paroxysmal auricular tachycardia has been described. The abnormal rhythm has persisted for seven months without intermissions, except those produced by treatment. Whatever may be the true explanation of the bizarre features presented by this case it is evident that an ectopic focus has come to dominate the heart, and only when the rate has been slowed, with difficulty, by the action of drugs can the sino-auricular node resume command.

We wish to thank Dr. P. Phillips, Superintendent, Southmead Hospital, Bristol, for permission to publish this case, and Professor C. Bruce Perry, and Dr. C. W. Curtis Bain for their help and advice.

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CONGENITAL HEART DISEASE WITH ISOLATED INVERSION OF THE ABDOMINAL VISCERA

BY

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From Guy's Hospital

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The two cases reported illustrate an uncommon type of partial inversion of the viscera, in which the abdominal organs alone are transposed while the heart remains in its normal position. Both were suffering from congenital heart disease, and a subsequent search brought to light several further reports of cardiac malformation associated with a similar transposition of the viscera. This combination cannot, therefore, be regarded as fortuitous, and, in fact, a similar and well-recognized relationship exists between congenital heart disease and another variety of incomplete heterotaxy, in which the heart alone is transposed. Isolated dextrocardia is the subject of two recent reviews, based on large series of cases collected from the literature (Roesler, 1930, and Lichtman, 1931); case reports of heart disease in the presence of isolated inversion of the abdominal viscera are, on the other hand, scanty and so far have not been critically reviewed.

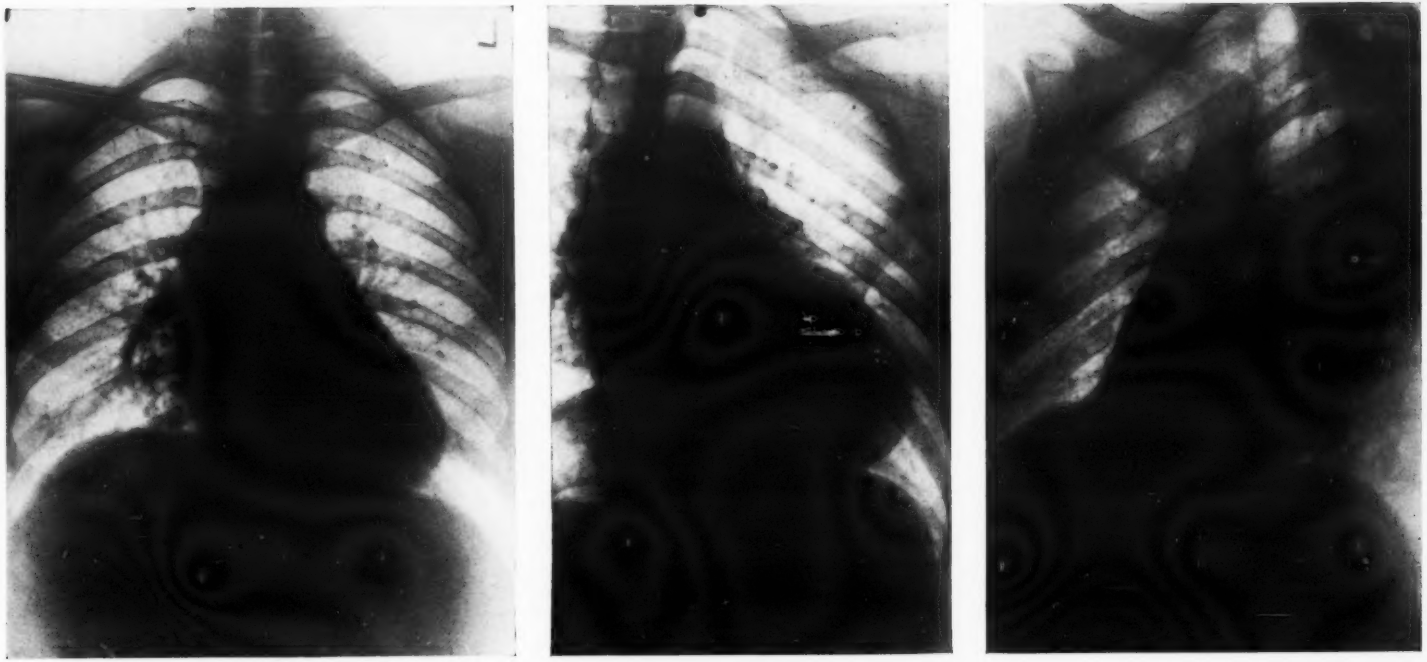
Case Reports

Case 1. An Army officer, aged 25 years, was admitted to Guy's Hospital in April 1946 for investigation. Suspicion about his heart arose two years earlier, when a routine radiogram of his chest showed a large heart. His capacity for exercise was normal; in fact, during the previous five years he had undergone several periods of very strenuous training without undue distress. There was no history of cyanosis and he had never suffered from rheumatic fever.

He was a well-developed fit-looking man, and was able to take vigorous exercise without dyspnœa. There was no cyanosis or clubbing of the fingers. He was apyrexial and his resting heart rate varied between 50–60, with striking sinus arrhythmia. Owing to this the blood pressure readings were somewhat variable and averaged 145/50. A very forcible apex beat was found 2·5 cm. outside the mid-clavicular line. A moderately loud, rough systolic murmur was audible in the second left intercostal space close to the sternum, conducted along that space, as well as to the back, just medially to the left scapula. The pulmonary second sound was accentuated and high pitched. The heart sounds were otherwise normal.

All other clinical findings were normal, except that the liver dullness was found in the left hypochondrium, while the right hypochondrium was resonant. Blood pressure readings in the lower limbs were equal to those in the arms and no anastomotic arteries were palpable over the chest wall.

X-ray findings. In the postero-anterior view (Fig. 1A) the heart was enlarged both to the left and to the right, with a maximum transverse diameter of 16 cm. in a chest of 29 cm. The convexity of the apical region suggested enlargement of the left ventricle, but the pulmonary conus was also abnormally prominent and the branches of the pulmonary artery, especially the right descending, were strikingly distended. The ascending aorta was displaced to the right; its right border lay 3·5 cm. from the mid-line. The gas bubble in the stomach was visible under the right diaphragm. On screening the lower third of the left border of the heart showed marked pulsation; systolic excursion in the region of the conus was also excessive, but no abnormal pulsation was visible in the hilar vessels.



A B C

FIG. 1.—(A) Case 1. Postero-anterior teleradiogram. Heart enlarged with increased convexity of the apical region. Enlargement of the conus and of the hilar vessels. Ascending aorta displaced to the right. The stomach lies under the right diaphragm.
(B) Case 1. Right (I) oblique view. Enlargement of the conus and of the hilar vessels.
(C) Case 1. Left (II) oblique view. Enlargement of the left ventricle. Right ventricle of normal size. Displacement of the aorta to the right.

The right (I) oblique view (Fig. 1B) confirmed the abnormal prominence of the pulmonary conus. The most striking feature of the left (II) oblique view (Fig. 1C) was bulging of the left border of the ventricular shadow, while the right border was, by contrast within normal limits.

The electrocardiogram (Fig. 2) showed sinus arrythmia, left axis deviation, and inversion of P II, P III, and T III.

Diagnosis. In view of the apparent enlargement of the left ventricle and the left axis deviation, the possibility of aortic regurgitation, sub-aortic stenosis, coarctation of the aorta, or of hypertension was considered, but no further evidence was found in favour of any of these conditions.

The prominence of the pulmonary conus, the widening of the main branches of the pulmonary artery, the forcible pulsation of the apex and of the conus, and the systolic murmur in the second left intercostal space with accentuation of the pulmonary second sound are in keeping with the diagnosis of an atrial septal defect. Left ventricular enlargement and left axis deviation are, on the

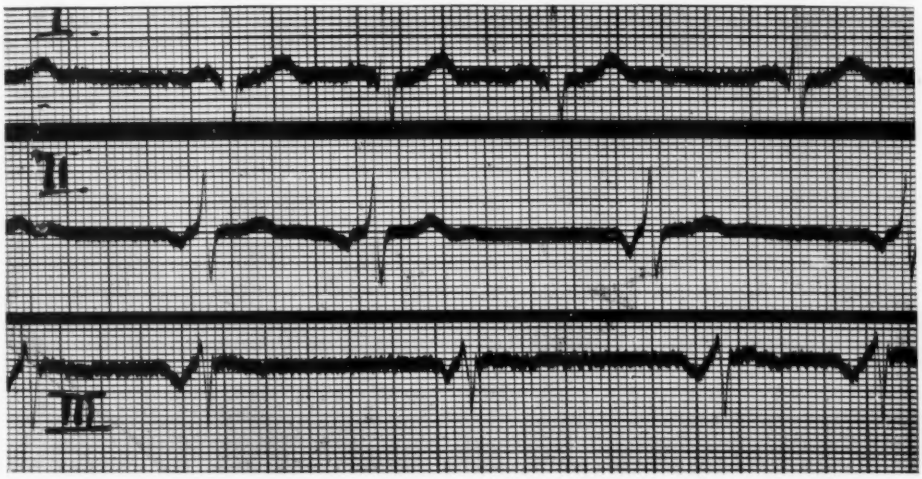


FIG. 2.—Case 1. Electrocardiogram, showing sinus arrhythmia, left axis deviation, inversion of P II, P III, and T III.

other hand, exceptional: in fact enlargement of the right ventricle and right axis deviation were found to be the rule in a series of 53 cases analysed by Bedford *et al.* (1940). A possible explanation of the anomaly is that in this case the ventricles are transposed and that the aorta, which is displaced towards the right, originates from an arterial right ventricle, the whole of the left border of the heart being formed by a venous left ventricle.

Some of the clinical findings, taken separately, would fit the diagnosis of pulmonary stenosis or of patent ductus arteriosus, but the evidence as a whole is against these, and the preponderance of the left ventricle would still remain unexplained. The most likely diagnosis is, therefore, patency of the atrial septum with corrected transposition of the great vessels, although it must remain speculative.

Case 2. A boy, aged 5 years, was admitted to the County Hospital, Farnborough, in May 1945, suffering from intestinal obstruction. He had been deeply cyanosed from birth, and clubbing of the fingers and toes had been present since early childhood. His capacity for exercise had always been much below normal.

On laparotomy he was found to have an ileo-cæcal intussusception, associated with non-rotation of the mid-gut. The cæcum was under the liver in the left upper compartment of the abdomen and the rest of the large intestine was displaced into the right half of the peritoneal cavity. The stomach was displaced to the right, and, as a later barium meal (Fig. 3) showed, its position was a mirror

image of the normal. Further details of the disposition of the abdominal viscera were published by van Meurs (1946).

The heart was moderately enlarged, with the apex beat 2 cm. outside the mid-clavicular line, and a strip of dullness for a distance of 1·5 cm. to the right of the sternum. A loud, rasping systolic murmur was heard over a wide area of the præcordium, with its maximum intensity in the third left intercostal space. The blood pressure was 90/60. The red cell count was 8·1 million with the hæmoglobin 130 per cent.

FIG. 3.—Case 2. Barium meal, showing reversed position of the stomach and jejunum.

FIG. 4.—Case 2. Postero-anterior teleradiogram. Cœur en sabot. Displacement of the aorta to the right. Double aortic arch.

X-ray findings. (Fig. 4.) The heart was moderately enlarged with a maximum transverse diameter of 11·5 cm. It was slightly displaced to the right: the right border of the ascending aorta was 4·5 cm. from the mid-line and part of the aortic arch appeared to the right of the trachea. 1·5 cm. higher, to the left of the trachea, there was another semicircular shadow, which possibly represented a second aortic arch.

Diagnosis. The deep cyanosis dating back to birth, with polycythæmia and clubbing of the fingers, is evidence of a congenital cardiac defect, with free mixing of blood between the right and left chambers. In view of the shape of the heart, the displacement of the aorta towards the right, and the loud systolic murmur in the third left intercostal space, the diagnosis of Fallot's tetralogy is highly probable.

SUMMARY OF REPORTED CASES AND DISCUSSION

A search produced only 12 further reported cases of congenital heart disease associated with isolated inversion of the abdominal viscera. Details of these are shown in Table I.

It would be unwise in this small series of cases to base an estimate of the total incidence

TABLE I

Author	Age and Sex	Type of Heart Disease	Abdominal Viscera	Autopsy
Breschet (1826) quoted by Gruber	6 weeks, M.	Cor biloculare	Stomach on the right. Liver central	Yes
Hickman (1869)	6 weeks, M.	Atria transposed Corrected transposition of the arterial trunks Patent atrial septum Patent ventricular septum Patent ductus arteriosus	Transposed	Yes
Marchand (1883) quoted by Gruber	1 day, ?	Cor triloculare biventriculare.	Stomach on the right. Liver on the right	Yes
Griffith (1897) quoted by Lichtman	9 months, M.	Atria transposed Transposition of the arterial trunks Patent ventricular septum Patent ductus arteriosus Pulmonary stenosis	Transposed	Yes
Lochte (1898)	17 years, M.	Atria transposed Transposition of the arterial trunks Patent atrial septum Patent ventricular septum Pulmonary stenosis	Stomach on the right. Liver central. The left lobe larger than the right lobe	Yes
Geipel (1899) quoted by Schelenz	Unknown	Atria transposed Aorta and pulmonary artery originate from the right ventricle	Stomach on the right. Liver on the right	Yes
Hingst (1901) quoted by Schelenz	Unknown	Patent atrial septum Patent ventricular septum	Spleen, liver, and stomach on the right	Yes
McCrae (1905)	49 days, M.	Atria transposed Patent atrial septum Patent ductus arteriosus Pulmonary atresia	Transposed	Yes
Royer and Wilson (1908)	6½ years, M.	Atria transposed Patent atrial septum Patent ventricular septum	Transposed	Yes
Knape (1912)	8 days, M.	Cor triloculare biatrium Atrial septal defect Pulmonary atresia Patent ductus arteriosus	Transposed	Yes
Shaw and Blake (1924)	2 years, M.	Patent ventricular septum	Transposed	No
Miller (1925)	10 weeks, F.	Atria transposed Patent atrial septum Patent ductus arteriosus Pulmonary artery and aorta arise from left ventricle	Transposed	Yes

of congenital heart disease, or of the relative frequency of the various types of cardiac defect in isolated inversion of the abdominal viscera. Although there are numerous surgical reports of transposition of the abdominal organs, the heart in these cases has not, as a rule, been examined with sufficient care to reveal minor abnormalities. Also, in the days before radiological study of heart disease was adopted, the abnormal position of the stomach is likely to have been often overlooked. For this reason, the prevalence of post-mortem records of severe heart lesions in this series may well give an unduly gloomy impression of this condition.

The prevalence of transposition of the atria is, however, very striking. Out of the 14 cases (including the 2 here reported) this otherwise rare abnormality was present in 8 cases: 2 of the remaining 6 had a common atrium supplying both ventricles, and in 4 the disposition of the atria could not be ascertained. It appears probable that this abnormality constitutes the key defect of the heart, the associated structural changes merely serving to direct the arterial and venous return to the heart into their correct outflow channels. Of the mechanisms by which this might be achieved, transposition of the aorta into the right ventricle and of the pulmonary artery into the left ventricle is alone completely effective. All other types of defect, such as patency of the septa or of the ductus arteriosus, merely provide for admixture of arterial to the venous blood of the systemic outflow, and are, therefore, incompatible with prolonged survival. In effect, in the whole series only two cases survived to adult age (Lochte, 17 years, and Forgacs, 26 years); in these subjects corrected transposition of the arterial trunks was diagnosed by post-mortem examination in the first, and on clinical grounds in the second. Of the remaining 12 cases, 6 died in the first few weeks of life and none of the others was over the age of seven at the time of observation.

The remarkable prevalence of transposition of the atria may offer a clue to the pathogenesis of the congenital heart lesions in this group and also in the very similar group of isolated dextrocardia. This type of heterotaxy, which is the exact reverse of the visceral arrangement under discussion, is nearly always complicated by congenital malformations of the heart. Lichtman (1931), in his survey of 161 reported cases of isolated dextrocardia, found only 3 examples of anatomically normal hearts. An interesting and significant fact emerges from Roesler's (1930) detailed analysis of 24 cases of isolated dextrocardia: the inferior vena cava terminated in the right atrium in 16 of the 18 in which the relevant data were available.

In an ideal mirror picture dextrocardia the vena cava runs into the left atrium; an arrangement which is the rule when both the heart and the abdominal viscera are transposed. In this group, as is well known, the heart is nearly always free from structural defect. If we accept such cases as the standard of the normal right-sided heart, it will be apparent that in Roesler's series the position of the atria is reversed. It may be stated, therefore, that when the abdominal viscera alone or the heart alone is transposed to the opposite side of the body, the arrangement of the atria is usually the reverse of the normal.

The similarity between the two groups of cases suggests a common pathogenesis of the cardiac defects. Of the many explanations put forward to account for the malformation of the heart in isolated dextrocardia, those which explain it as a result of torsion (Pal, 1907) or those which assume the heart lesions to be primary and the transposition of the heart as an effect of these (Monckeberg, 1915) are clearly not applicable to isolated transposition of the abdominal viscera, in which the heart remains in its normal position. A satisfactory hypothesis, valid for both groups, must take into account the abnormal relative position of the abdominal viscera and the heart. The only conceivable mechanism by which the position of the abdominal organs might influence the structure of the heart is through the agency of the embryonic abdominal venous channels.

To make the argument clearer, it is useful to recall that the original symmetry of the

sinus venosus of the embryo is later destroyed by the disproportionately rapid increase in size of the right horn of the sinus. This structure is subsequently incorporated into the primitive atrium and eventually forms part of the right atrium of the mature fœtus. The rapid growth of the right horn of the sinus is determined by the development of transverse anastomoses in the abdominal venous channels shunting blood from the left side of the abdomen to the veins on the right, which terminate in the right horn of the sinus. Finally the veins on the left disappear, and the whole of the inflow from the liver and the placenta is delivered into the right atrium by way of the vena hepatis communis. This vein is later incorporated into, and forms, the terminal portion of the inferior vena cava.

It is clear, therefore, that the abdomina venous channels of the embryo have a profound influence in determining the development of the atria. It seems probable that the reversal of the normal relationship between the heart and the liver in the two varieties of incomplete heterotaxy is associated with a corresponding change in the hepatic venous channels; a possibility discussed in detail by Lochte (1898). In the event of such a change the "left" horn of the sinus venosus would receive the venous return from the liver and placenta, and in the course of embryonic development, the inferior vena cava would come to terminate in the "left" atrium.

The transposition of the atria, which may be regarded as the fundamental defect in most cases of isolated inversion of the abdominal viscera and of isolated dextrocardia, is then a necessary sequel of the reversed connection between the abdominal veins and the sinus venosus. The associated malformations of the heart occur, as already suggested, as a result of the faulty development of the cardiac septa, or of an incomplete torsion of the aorto-pulmonary septum, in an attempt to divert the venous return into its correct outflow channel.

Summary

Two cases of congenital heart disease associated with isolated inversion of the abdominal viscera are described, together with a summary of similar cases that have been reported.

An attempt is made to correlate the findings in this group with those in isolated dextrocardia.

I am indebted to Dr. Maurice Campbell, under whose care Case 1 was investigated, for much help and encouragement. My thanks are also due to Dr. J. F. Hackwood, Medical Superintendent of the County Hospital, Farnborough, for his permission to report Case 2, and to Mr. D. P. van Meurs for his kindness in lending me his records of the laparotomy findings.

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SUBACUTE BACTERIAL ENDOCARDITIS WITH ONSET AS OPTIC NEURITIS

BY

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From St. George's Hospital

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Although retinitis, optic neuritis, or " choked disc " occurring in the course of subacute bacterial endocarditis is not uncommon (Kimmelstiel, 1928), complaint of visual abnormality or the finding or papillœdema as an initial or early manifestation of the disease is not usual. The two following cases presented difficulty in diagnosis by the predominantly neurological picture, emphasized by involvement of the optic nerve.

Case 1. *Retrobular neuritis with subacute bacterial endocarditis*

A housewife, aged 30, was admitted to hospital with a story of increasingly misty vision in the right eye. At the age of 10 she had rheumatic fever and later during convalescence involvement of the aortic valve was noted. Since the birth of her first child by Caesarean section one year previously she had not felt completely well and had become easily fatigued, but there was no undue dyspnœa and she was able to swim and dance without inconvenience. One month before admission she noted black spots before the right eye followed by blurring of vision. There had not been limb weakness, diplopia, or abnormality in micturition.

Examination showed a well-built, somewhat obese young woman. There was a left internal rectus weakness (present since childhood) and blurring of the outline of the right optic disc. There was no gross defect of the visual fields on confrontation and the central nervous system otherwise showed no abnormality. There was a " collapsing " pulse, cardiac enlargement to the left with impulse four and three-quarter inches from the mid-line in the fifth left interspace, and aortic diastolic and systolic bruits. The blood pressure was 165/60. There were no signs of cardiac failure, except that the liver edge was palpable and tender one finger's breadth below the right costal margin. The cerebrospinal fluid at an initial pressure of 230 mm. was otherwise normal. The Wassermann reaction in the blood and C.S.F. was negative. The blood sedimentation rate was 6 mm. in the first hour. The urine was normal clinically and microscopically.

On X-ray screening there was enlargement of the left ventricle. An electrocardiogram showed splintering of R III, depression of S–T II, and inversion of T II and T III.

During one week in hospital there was no fever. The patient was discharged with a diagnosis of retrobulbar neuritis and rheumatic carditis (aortic reflux).

Eight months later she was again admitted to hospital. The amblyopia had disappeared within a month of her previous admission and for four months she had remained in fair health, until following a dental abscess she complained of headache, sweats, and increasing lassitude. There had been irregular fever, usually in the afternoon; nevertheless she continued at her household duties. For two days before admission she had noted painful spots in the palms of the hands.

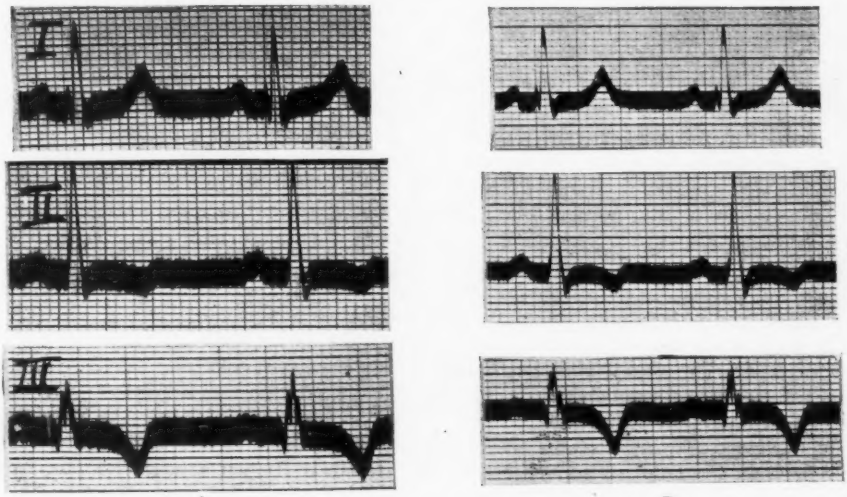
Clinical examination showed a temperature of 101° F., two Osler's nodes in the palm of the right hand, and two petechiæ over the right shin. There was no finger clubbing. Apart from tachycardia the cardiovascular signs (cardiac enlargement with aortic reflux) remained unchanged. The liver was no longer palpable but the spleen was now one finger's breadth

below the costal margin. There was some pallor of the right optic disc and a small hæmorrhage in the right optic fundus; there were no other abnormal neurological findings.

Blood culture on three successive days grew *Streptococcus viridans* (penicillin sensitive). The red blood corpuscles were 4,100,000, the hæmoglobin 80 per cent, the white blood corpuscles were 9,600—polymorphs 73 per cent, lymphocytes 23 per cent, and mononuclears 4 per cent.

The urinary deposit showed red blood cells.

For the four days prior to treatment with penicillin the temperature was of the picket fence type. The fever responded to penicillin within twenty-four hours but during the first week of treatment a splenic infarct occurred and Osler's nodes appeared at intervals. In the



A B

FIG. 1.—Electrocardiograms of Case 1. (A) During the retrobulbar neuritis. (B) One year later when symptom free.

third week of treatment there was sudden onset of motor aphasia (the B.S.R. at this time was 3 mm.). The total dosage of penicillin was seven million units over 30 days. Before discharge from hospital repeated blood cultures were sterile.

Three months later she reported herself as well, and the speech was normal except for an occasional hesitancy.

Comment. Presumably the retrobulbar neuritis was of embolic origin although examination at the time did not suggest any such dramatic event.

It is tempting to interpret the changes in the cardiogram (Fig. 1) as the result of a posterior infarction ; however, there is nothing to substantiate this clinically and serial cardiograms over a period of a year have shown little change in the contours, so that the aortic reflux alone is the likely cause of this ischæmic posterior coronary pattern.

The peculiar interest of the case is the unusual neurological presentation of subacute bacterial endocarditis and the lengthy latent period before general signs became apparent. At her first admission the retrobulbar neuritis was considered of the usual unknown ætiology there being no other embolic or toxæmic manifestation. Perhaps the onset of the disease, as evidenced by undue fatigue, dates from the birth of her child some sixteen months before frank symptoms; alternatively it may be suggested that the bacterial endocarditis dates only from

the dental abscess which would entail a second pathology for the retrobulbar neuritis, a less attractive supposition.

Case 2. *Subacute bacterial endocarditis with papillœdema, mimicking intracranial tumour.*

A married woman, aged 25, was admitted to hospital with a history of left hemiplegia of sudden onset. At the age of ten she had rheumatic fever which left in its train a heart murmur.

One week before admission there was severe epigastric pain followed two days later by numbness of the left side of the mouth, and the next morning she discovered her left side paralysed and anæsthetic. Eighteen months previously and coincident with the first pregnancy, she noted generalized vertical headaches; these were less evident after a miscarriage at ten weeks. Two months before admission, when she was again pregnant, she experienced troublesome right occipital headaches for two weeks, which recurred with the onset of the hemiplegia. One month ago there had been sudden pain in the left lower jaw with trismus lasting for a week. There had recently been some deterioration in vision.

Physical examination showed a left hemiplegia with maximum weakness in the left arm. The tendon reflexes were sluggish; there were a left Babinski, left hypoæsthesia, and a disordered response to pinprick on the left side. There was bilateral papillœdema, more marked on the left, with great engorgement of the retinal veins. There was no aphasia.

The temperature was normal; the heart was not apparently enlarged; rate, rhythm, and sounds were normal; at the apex there was a blowing systolic murmur. The blood pressure was 120/90. She was eight weeks pregnant.

There was a tender swelling over the horizontal ramus of the left mandible without obvious dental cause, and radiographs of the mandible showed no abnormality.

The urine at first showed no abnormality but later there were occasional granular casts and a few red cells. The hæmoglobin was 70 per cent; the red cells 4,450,000, and the white cells 16,000 with 84 per cent polymorphs. The blood sedimentation rate was 60 mm. in the first hour. Repeated blood cultures were sterile.

The headache and papillœdema increased; vomiting later became frequent. A month after admission she suddenly complained of paræsthesiæ in the left hand with motor aphasia accompanied by an indescribable mental state, all of short duration. Ventriculography showed no abnormality. After three months of progressive deterioration the illness ended in bronchopneumonia. The temperature apart from an occasional rise to 99° to 100° F. at noon had shown little abnormal until the pre-terminal fever.

Autopsy. This revealed a small yellow area of necrosis in the posterior limb of the right internal capsule encroaching on the optic thalamus, a more recent infarct one inch in diameter in the right occipital lobe, and the most recent lesion two inches in diameter in the left parietal lobe.

The heart showed moderate dilatation of all its chambers. There was thickening and distortion of the anterior cusp of the mitral valve but there was no true stenosis. Mural endocarditis was present on the posterior wall of the left auricle. There were old infarctions in both kidneys and there was a single infarct in the spleen. The liver was enlarged and congested.

There were pleural adhesions over the right lung and early bronchopneumonia was present. The uterus contained a healthy male fœtus of 4 to 5 months.

Comment. Here the antecedent period before gross embolic manifestation was probably eighteen months. At admission the picture was so dominated by the " choked discs " that the tentative diagnosis was intracranial tumour, in support of which were the progressive nature of the papillœdema and later vomiting. The possibility of bacterial endocarditis was entertained, but repeatedly negative blood cultures and the absence of fever, of splenomegaly, and of skin emboli obscured the true aetiology of the neurological findings. The presence of an old rheumatic valvular lesion was of paramount diagnostic significance.

Discussion

Over an eight-year period there were 26 patients admitted to St. George's Hospital who showed unequivocal evidence of subacute bacterial endocarditis. Among these were 5 patients in whom note of ocular symptoms was made ; 3 showed hæmorrhage into the fundus oculi and the 2 with involvement of the optic nerve are here recorded. Krinsky and Merritt (1938) considered that 20 of their series of 100 cases of bacterial endocarditis showed a picture so predominantly neurological that the primary lesion was thought to lie in the central nervous system. They noted that 10 per cent of patients complained of visual disturbance at some stage of the disease, compared with headache the most common neurological symptom, which occurred in 24 per cent ; " choked discs " were observed in 8 per cent. They describe a slowly developing hemiplegia with mixed aphasia and left hypoalgesia in a left-handed male where progressive papillœdema appeared to support the diagnosis of tumour ; later fever, petechiæ, valvular involvement, and a positive blood culture established the true ætiology. In a further patient amblyopia had occurred some months before admission with hemiplegia, the result of endocarditis lenta.

As embolism is the essential feature of the symptomatology of subacute bacterial endocarditis and as death from cerebral embolism occurs in 23 per cent (Blumer, 1923), it is surprising that bizarre neurological and psychiatric complications are not more common. Kernohan *et al.* (1939) report that in every case of subacute bacterial endocarditis in which they examined the brain microscopically, widespread reactions associated with occluded arterioles or capillaries were found. The lesions were the result either of embolism, in which the endothelium of the intima surrounded the blood.clot, or of thrombosis *in situ*, in which the initial lesion consisted of a hyaline change in the vessel wall progressing to partial occlusion of the lumen and here endothelial cells were present in the middle of hyaline thrombus. These latter changes they attribute to cocci or the local effect or their toxins.

Changes in the optic nerve are the result of occlusion in part of the blood supply, which gives rise to swelling of the nerve, lying for most of its course in the unyielding surroundings of the optic foramen. It is, therefore, a matter of the degree of occlusion and subsequent swelling whether retrobulbar neuritis with slight blurring of the disc outline or gross papillœdema with obstruction of the retinal veins occurs. Spread of intravascular clotting or repeated embolism is presumably the cause of the progressive nature of the papillœdema, which seems to be characteristic. Theoretically there is no reason why the choked disc should not be unilateral, although it is probable that where repeated embolism has occurred in one optic nerve the other nerve is unlikely to remain unscathed.

The practical conclusion from the reported cases is that where rheumatic or congenital heart disease exists in the presence of neurological findings, particularly where these are of sudden onset, endocarditis lenta is a very real possibility; the absence of other contributory evidence is not exclusive of this diagnosis.

Summary

Two cases of subacute bacterial endocarditis with early involvement of the optic nerve are described and the difficulty in diagnosis emphasized. Neurological presentation of the disease is not uncommon, and optic neuritis, even of a progressive nature, is not an incompatible finding.

I am indebted to Dr. Anthony Feiling and to Dr. C. B. Levick for permission to publish these cases.

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PENICILLIN TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

BY

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The early impression that penicillin was ineffective in subacute bacterial endocarditis arose from the first case treated, that of Florey and Florey (1943), and from the 17 cases unsuccessfully treated by Keefer *et al.* (1943). In the following year Loewe *et al.* (1944) recorded 7 apparently successful cases, but the period of observation was very short. More failures followed (Herrell, 1944; Herrell *et al.*, 1944; Bloomfield *et al.*, 1944), but Dawson and Hobby

TABLE I

CASES OF SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN: REPORTED BETWEEN JANUARY 1945 AND AUGUST 1946

Reference	Number of cases	Number of cases alive and free from infection	Period of observation after treatment (months)
Bloomfield, Armstrong, and Kirby (1945)	11*	9	1–6
Bloomfield and Halpern (1945)	18†	18	3–17
Christie (1946)	147‡	81	3–8
Dawson and Hunter (1946)	35§	30	3–32
Favour, Janeway, Gibson, and Levine (1946)	17	11	6–18
Flippin, Mayock, Murphy, and Wolferth (1945)	20	12	2–17
Glaser, Smith, Harford, and Wood (1946)	22	13	1–24
Goerner, Geiger, and Blake (1945)	16	11	3–13
Levy and McKrill (1946)	11	6	11–18
Loewe (1945)	54	37	2–15
Meads, Harris, and Finland (1945)	9	7	1–11
Mokotoff, Brams, Katz, and Howell (1946)	17	13	8–20
White, Mathews, and Evans (1945)	9	6	2–8
Various:—Anderson and Keefer (1945); Geiger and Goerner (1946); Hines and Kessler (1945); Kelson (1945); Paullin and McLouglin (1945); Russek *et al.* (1945); Vesell and Kross (1946)	20	12	various
Totals	406	266	

* Favourable cases selected, with 3 exceptions.

† Favourable cases selected; an unstated number previously reported were included.

‡ Collected British cases including 18 cases of Ward, Meanock, Selbie, and Simon (1946) and 20 cases of Sanderson and McEntegart (1946).

§ First 5 cases selected as favourable, and 30 unselected except organism penicillin-sensitive.

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(1944) were successful in 3 of 10 cases. At this time Keefer (1944) stated that of 55 cases treated in the United States only 3 were alive a year later.

By 1945 it was realized that to be successful penicillin must be administered in large doses for long periods; Keefer (1945) suggested 200,000 to 300,000 units daily for 3 weeks, Loewe (1945) advised up to 1,000,000 units daily for 5 weeks and Bloomfield *et al.* (1945) gave 200,000 units daily for 6 to 8 weeks. The subsequent results have been considerably better and, since the beginning of 1945, reports of 406 cases with 266 recoveries have been published in this country and in the United States; these are summarized in Table I. In some instances the results are not representative of the value of penicillin in unselected cases for, owing to shortage of penicillin at the time, those likely to benefit from treatment were chosen.

Early in 1945 the Medical Research Council initiated a coordinated investigation at 12 centres in Britain, and Christie (1946) has published a summary of the results in the first 147 unselected cases with 81 recoveries. At the Manchester centre 40 have so far been treated; 7 of these, in which treatment was completed less than six months ago, are excluded. This period has been selected because in published cases, death has so far not occurred more than six months after successful treatment except from heart failure or unrelated causes. Only those in which the causative organism was isolated are included, but otherwise there has been no selection ; 2 patients were moribund on admission and in 1 the infecting organism was insensitive to penicillin.

Some Clinical Features Before Treatment

Of 33 patients, 11 were male and 22 female; their ages ranged from 13 to 59.

Capacity for Effort before Infection. Subacute bacterial endocarditis rarely develops when rheumatic or congenital heart disease is severe (Libman and Friedberg, 1942); none of our patients had auricular fibrillation or a history of heart failure prior to infection and all were either in employment or looked after their homes and families or studied at school or college (Table II). In only 3 cases had there been considerable impairment of capacity for effort

TABLE II

Capacity for Effort and Occupation Before Infection

Capacity for effort	Number of cases	Sedentary employment	Non-sedentary employment	Housework	School or college
Class I	17	4	7	4	2
Class II	13	2	4	7	—
Class III	3	1	—	2	—
Totals	33	7	11	13	2

before infection (Class III); in 13 cases some dyspnœa had occurred on unusual exertion but not during ordinary activity (Class II); in 17 cases no symptoms had been noticed on exertion and 8 of these patients had been unaware of their cardiac lesion (Class I). The classification used in that accepted by the American Heart Association (*Criteria for Nomenclature and Diagnosis*, 1942).

Physical Signs of Underlying Heart Disease. Rheumatic heart disease was present in 28 and congenital heart disease in 4 cases; in one both congenital and rheumatic lesions were found at necropsy. In 11 of our 29 rheumatic cases only systolic murmurs were present on admission and we have been impressed by the rarity of the typical presystolic murmur when

bacterial endocarditis is present. Although radioscopy sometimes showed pulmonary congestion and enlargement of the right ventricle consistent with well-developed mitral stenosis, we believe that the rarity of the characteristic physical signs is principally because only slight mitral lesions were present in most cases, for mitral stenosis was present in only 2 of 12 cases with rheumatic heart disease that came to necropsy. Aortic incompetence, however, appeared to be disproportionately common, for it was present clinically in 16 of 29 rheumatic cases. This high proportion may be due to the tendency for subacute bacterial endocarditis to attack the aortic valve, so that some aortic lesions may have arisen from the infection and not from the underlying rheumatic heart disease.

Thus, in this series, both the good capacity for effort before infection and the nature of the rheumatic valvular lesions support the view that the underlying heart disease was usually relatively slight.

The Onset of Bacterial Endocarditis. This occurred during pregnancy or at confinement in 7 cases, nearly one-third of our female cases. In 3 cases symptoms of infection were first noticed, two, six, and nine weeks after dental extractions.

The initial symptoms of bacterial endocarditis rarely give any indication of the nature of the infection (Christian, 1941); in our cases the commonest presenting features were lassitude (10 cases), generalized " rheumatic " pains (6), pyrexia in patients already under observation (6), or a vague illness resembling influenza (5 cases). In 3 cases major embolic accidents marked the onset of symptoms; in one a subarachnoid hæmorrhage was presumably due to rupture of a mycotic cerebral aneurysm; in a second hæmoptysis from a pulmonary infarct led to a mistaken diagnosis of pulmonary tuberculosis, and in the third visible hæmaturia and loin pain from a large renal infarct suggested the presence of a urinary calculus. Persistent sweating (twice) and pallor (once) were the presenting symptoms in the other 3 cases.

The subsequent symptoms were protean. Loss of weight occurred in every case but was often not noticed until several months after the onset of the infection. Generalized " rheumatic " pains developed at some stage in 17 cases. These pains were sudden in onset but fleeting in character; they were rarely confined to the joints but often affected muscle masses in the limbs or trunk. They sometimes led to a mistaken diagnosis of " rheumatism " or rheumatic fever. Pain persisting in one site, presumably embolic in origin, was noticed in 21 cases; in 9 in a limb, in 5 in the splenic area, in 4 in the chest, in 2 in the lumbar area and in 1 severe central abdominal pain persisted for several weeks. Nausea and vomiting were common, and persistent sweating was noticed in 15 and rigors in 4 cases. Progressive impairment of capacity for effort was a feature in 16 and was followed by heart failure in 15; this was usually a late feature of cases in which the diagnosis was delayed.

In over one-third of our cases (13) symptoms had been present for twenty or more weeks before treatment.

In addition to the 3 cases in which symptoms of bacterial endocarditis followed dental extraction, teeth were extracted after the onset of bacterial endocarditis in 2 others, and paradontal sepsis was present in 9 others. Tonsillar sepsis was found in 4 and cholecystitis in 1 case. The frequency of paradontal and tonsillar sepsis in this series supports the suggestion that the mouth and pharynx are often the sites from which the cardiac infection arises but, since *Strept. viridans* can be grown from the normal mouth, it did not seem worthwhile to attempt to compare the organism grown from the blood with the flora of the mouth and pharynx.

Sulphonamides had been given to 15 cases before admission; in all these the causative organism was subsequently isolated from the blood.

Investigations

The scheme of investigation is detailed in Table III.

Blood Cultures were made without regard to the temperature of the patient by the method of Penfold, Goldman, and Fairbrother (1940): 7 c.c. of blood was withdrawn from a vein into a sterile oil-free syringe; 2 c.c. was introduced into a small vial containing a balanced oxalate mixture (Wintrobe and Landsberg, 1935) and reserved for the erythrocyte sedimentation rate; 1 c.c. was added to 4 c.c. glucose trypsin broth and 1 c.c. to 4 c.c. saponin broth; with these pour plates were made using melted agar. The remaining 3 c.c. was added to 50 c.c. of Hartley digest broth. The inoculated media were incubated at 37° C. under atmospheric conditions and kept 14 days before a final negative report was given. If negative, further cultures were incubated in an atmosphere of 10 per cent CO_2 as it was found that several strains grew more readily, or could only be grown, under these conditions: this technique was later adopted in all cases. To cultures taken during penicillin therapy sufficient penicillinase (prepared by the method of Duthie, 1944) was added to neutralize a concentration of at least 10 units of penicillin per c.c. of blood.

TABLE III

Scheme of Investigation

Before treatment	During treatment	After treatment
Cardioscopy	Cardioscopy, Cardiogram — At end of treatment.	Cardioscopy, Cardiogram — At intervals.
Cardiogram		
Blood culture	Blood culture	Blood culture — In first week; every two weeks in hospital, if apyrexial; monthly after discharge.
Full blood count	Hæmoglobin and total white count	Hæmoglobin and total white count
Sedimentation rate	Sedimentation rate — Weekly.	Sedimentation rate
Microscopy urinary deposit	Microscopy urinary deposit	Microscopy urinary deposit
Urea clearance	Urea clearance, Blood urea — If indicated.	Urea clearance, Blood urea — If previously abnormal.
Blood urea		
Bacteriology of urine	Serum penicillin levels (three times weekly)	

In 16 of 33 cases positive blood cultures had been obtained before admission, in 5 repeated cultures had been negative, and in 12 no culture had been attempted. On admission a positive culture was obtained at the first attempt in 29 and on the second attempt in the remaining 4 cases. In only one, admitted with suspected bacterial endocarditis during this investigation, were we unable to isolate an organism; that case is, therefore, not included in this series. Using the technique we have described it is rare to encounter difficulty in isolating the organism in clinical cases of bacterial endocarditis.

Strept. viridans was isolated in 26 and non-hæmolytic streptococci in 5 cases; in 1 of the remaining 2 the organism was *Hæmophilus influenzæ* and in the other case a *Pneumococcus* was isolated.

TABLE IV

Coefficients of Resistance of Infecting Organisms

Organism	Number of cases	Coefficient of resistance		
		<0·5	0·5–4·0	>4·0
Streptococcus viridans	26	6	18	2
Non-hæmolytic streptococcus	5	3	2	—
Hæmophilus influenzæ	1	—	—	1
Pneumococcus	1	Not tested quantitatively		

Coefficients of Resistance of the Organisms. Two sets of tubes were prepared with twofold decreasing dilutions of a nutrient broth containing a known concentration of penicillin. Each tube of one set was inoculated with a standard drop of a 24-hour broth culture of *Staph. pyogenes* (Oxford " H " strain) and to each tube of the other set a drop of a broth suspension of the test organism was added. All tubes were incubated overnight and the resistance of the organism to penicillin estimated by comparing the concentration of penicillin necessary to inhibit its growth with the concentration that inhibited growth of the Oxford staphylococcus; the resistance of the test organism was expressed as a multiple of the resistance of the Oxford staphylococcus. Our observations are summarized in Table IV.

Penicillin Serum Levels. The penicillin level in the blood was estimated in a similar way, but in one set of tubes the patient's serum was used instead of the penicillin solution and all tubes were inoculated with the Oxford staphylococcus. The bacteriostatic activity of the patient's serum was thus compared with that of known concentrations of penicillin.

These methods of estimating the resistance of the organism and the penicillin serum level are open to criticism. Although standard solutions of penicillin do not contain less than the stated amount, they may contain rather more and this will lead to an underestimate of the penicillin serum level. The penicillin sensitivity of the Oxford staphylococcus varies in subculture and is not an altogether reliable standard for assessing the resistance of the test organism. Similar difficulties have been encountered by Glaser *et al.* (1946). The principal value of these tests lies in their ability to recognize insensitive organisms and to indicate whether the patient's blood is bacteriostatic.

Blood Counts and Sedimentation Rate. At first the sedimentation rate was estimated using a Wintrobe tube; later the reading was corrected by the method of Wintrobe and Landsberg (1935). The uncorrected rate was invariably raised before treatment but, of 13 cases in which a correction from the hæmatocrit reading was applied, 1 was within normal limits and 2 were high normals (12 and 14 mm. in the first hour).

In 24, the hæmoglobin on the Haldane standard was less than 70 per cent on admission and less than 50 per cent in 8 cases. On admission an increase in the number of polymorphonuclear leucocytes was found in 26; this was not always revealed by a total leucocyte count, which was increased in only 14 cases.

Cardiac and Renal Investigations. There were 28 patients who were fit for 6 ft. teleradiograms before treatment; in 8 the heart was not appreciably enlarged, in 13 the cardiothoracic ratio was between 1·9 and 1·6, and in 7 gross enlargement was present (cardiothoracic ratio 1·5 or less).

Cardiograms were taken before treatment in 32 cases; 13 were within normal limits, including 6 with left axis deviation and aortic incompetence. The principal abnormalities were prolonged P–R in 1, right axis deviation in 2, left ventricular strain in 9, low voltage QRS (all leads) in 2, low voltage T (all leads) in 5, right B.B.Bl. in 1, and dextrocardia in 1 case (more than one abnormality were present in 2 cases). The infrequency of right axis deviation is further confirmation of the absence of severe mitral lesions in these cases.

We have accepted as abnormal a blood urea of more than 40 mg. per 100 c.c. and a standard urea clearance of less than 70 per cent. When the urinary deposit contained a few red cells with, usually, a few leucocytes and granular and cellular casts, we have classified the abnormality as " slight," whereas when many red cells were visible as a naked-eye deposit, usually accompanied by many leucocytes and casts, we have described the abnormality as " gross." By these criteria, the renal function was impaired in 10 cases, whereas the urinary deposit was always abnormal, the changes being " slight " in 19 and " gross " in 14 cases.

Treatment

Apart from the treatment of heart failure, of anæmia, and of focal sepsis, the only therapeutic measure used in these cases was the administration of penicillin.

At first various schemes were adopted to determine the duration of treatment and the dosage of penicillin necessary to control the infection; these experiments were conducted at all centres and the results have been summarized by Christie (1946). The most satisfactory course for initial treatment was 0·5 mega unit daily for 28 days. Since relapses in some of

the earlier cases were subsequently treated by a full course, and because the 28-day course was adopted very early at this centre, it happens that, of 25 of our cases who lived to complete treatment, only 3 did not receive the full course of 0·5 mega unit (or more) daily for 28 days. Of these 3, one was the first in this series and died before we adopted the longer course; one, who remains well, refused treatment after two courses of nine and ten days, and in one treatment had to be stopped after three weeks owing to severe thrombopenia; this patient died four weeks later from heart failure with her infection apparently controlled. Treatment known to be inadequate does not, therefore, play an important part in assessing the results in these cases.

Penicillin is remarkably free from undesirable toxic effects but, in this series, the need to give large doses for several weeks afforded a useful opportunity to study such effects. In the earlier cases we noticed that, although the temperature rapidly became normal after starting treatment, it often rose again at the beginning of the second week and an intermittent pyrexia persisted until penicillin therapy ended (Fig. 1, Case 24). During the fourth week of therapy

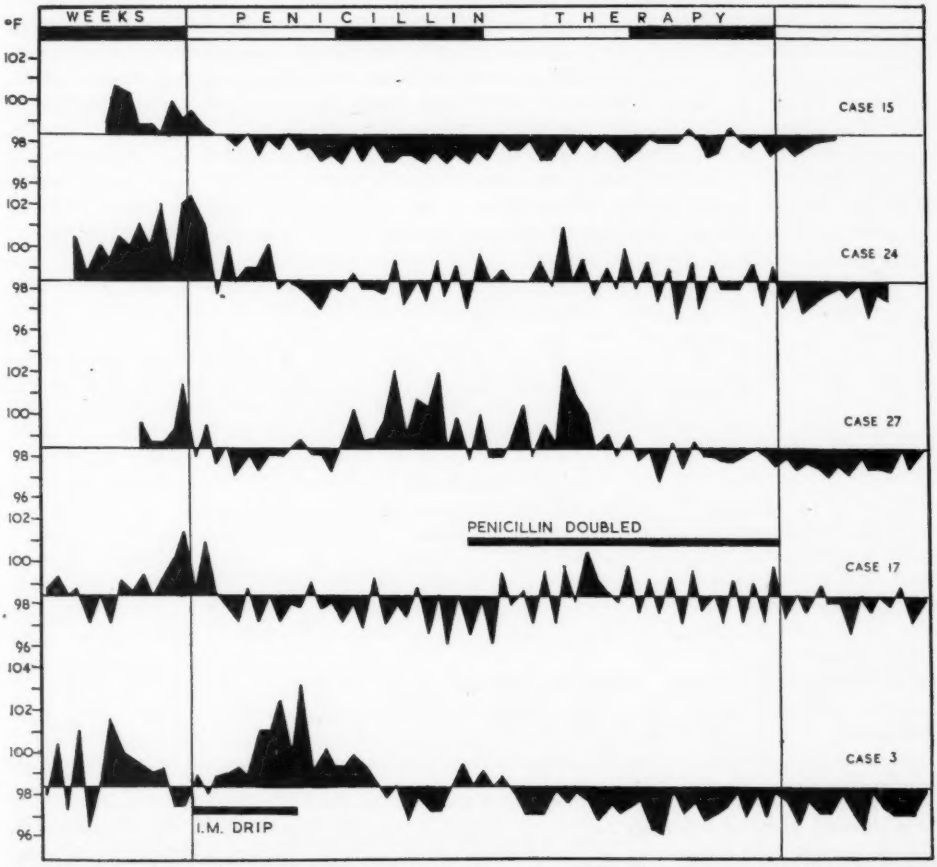


FIG. 1.—Temperature Charts during Treatment. Case 15. Uncomplicated response—apyrexial after first two days. Cases 24, 27, and 17. Penicillin pyrexia. Case 3. Pyrexia due to intramuscular drip, settling when method of administration changed to three-hourly injections.

the pyrexia tended to diminish and sometimes disappeared (Fig. 1, Case 27). At first we were inclined to suspect that such pyrexia was due to failure to control the infection and this led us to double the dose of penicillin in 3 cases, but the pyrexia then became more striking (Fig. 1, Case 17). Pyrexia of this type was noticed in 13 cases and in every case it disappeared when penicillin was discontinued. We conclude that when the temperature falls to normal in the first week, a subsequent rise in the second week, which either persists until penicillin is stopped or disappears during the fourth week of treatment, can be regarded as a drug fever. More highly purified penicillin became available later but this did not reduce the incidence of penicillin pyrexia which developed in 5 of the first 17 and in 8 of the last 16 cases. We are, therefore, inclined to attribute the pyrexia to penicillin itself and not to impurities. Penicillin pyrexia is of no prognostic significance, for of these 13 cases only 3 died. Recurrence of pyrexia during treatment has been previously recorded by Dawson and Hobby (1944), Anderson and Keefer (1945), Bloomfield and Halpern (1945), Meads *et al.* (1945), and Bloomfield *et al.* (1945); it has usually been attributed to emboli, infection by injections or drips, or to absorption of healing lesions, but Dawson and Hobby (1944) and Bloomfield and Halpern (1945) considered it might be due to penicillin or an associated impurity. It is agreed that pyrexia during treatment does not necessarily indicate failure to control the infection.

In 2 cases an urticarial rash developed during the third week of treatment and disappeared a few days after the end of treatment. Urticarial rashes have been previously described by Keefer *et al.* (1943), Bloomfield *et al.* (1945), Mokotoff *et al.* (1946), and Geiger and Goerner (1946). In one case bruising in several parts of the body was noticed on the fourteenth day of treatment and the platelet count was 50,000 per c.mm.; a week later the count had fallen to 35,000, and it seemed best to stop treatment; the count then increased slowly to 58,000 before death four weeks later. In another case the platelet count was 95,000 before death on the twentieth day of treatment.

We have usually given penicillin by three-hourly intramuscular injection and this has been well tolerated for long periods; only one patient refused to continue treatment for the prescribed time. In 5 cases, however, we used a continuous intramuscular drip, changing the site every 24 hours; but in each case, after a few days, we were obliged to change to three-hourly injections owing to severe pain at the site of injection and the development of pyrexia (Fig. 1, Case 3). In all these cases the penicillin was of the less purified type and we have not tested this method using the more highly purified preparations now available.

TABLE V

AVERAGE PENICILLIN SERUM LEVELS WITH 0·5 MEGA UNIT DAILY

Time after injection	Number of cases	Penicillin serum level in units per c.c.				
		<1	1–3	3–5	5–10	>10
Half an hour	31	1	13	11	5	1
		<0·1	0·1–0·5	0·5–1	1–5	>5
Three hours	29	3	9	7	8	2

Penicillin serum levels were estimated half an hour and three hours after the injection. All our patients received 0·5 mega unit daily and the figures given in Table V are averages of the levels reached with that dose. In 2 with severe renal failure, penicillin retention led to three-hour serum levels of 12 and 8 units per c.c.; a similar observation was made by Sanderson and McEntegart (1946). We have not been able to correlate the penicillin level with the outcome

of treatment but the levels attained appear to be bacteriostatic for all except the most insensitive organisms (Table V).

Dental and Tonsillar Infection. On admission tonsillar sepsis was present in 4 cases; 2 of these died and in the other 2 tonsillectomy was undertaken during convalescence, 0·5 mega unit of penicillin being given daily for two days before and three days after operation. On admission there was clinical or radiographic evidence of paradontal infection in 9 cases; in 4 of these treatment was undertaken during the third or fourth weeks of penicillin therapy and in 4 with penicillin cover during convalescence; 1 patient refused dental treatment. In all 10 cases in which focal sepsis was treated under penicillin cover there was no post-operative pyrexia and blood cultures remained sterile. We now prefer to eradicate focal sepsis during penicillin treatment of the bacterial endocarditis, for reinfection is possible if septic foci are still present when penicillin is discontinued.

Results of Treatment

Of 33 patients treated, 15 have died and 18 are alive and free from signs of infection; 9 for 6 to 12 months after the completion of treatment, 7 for 12 to 18 months, and 2 for over 18 months. In discussing these results in detail it is convenient to consider separately the successful and the unsuccessful cases for different problems have been investigated in each group; in successful cases we have been interested principally in studying the response to treatment and the degree of recovery which has been achieved, whereas, in those unsuccessful cases in which death occurred from heart failure, uræmia, or vascular accidents, despite control of the infection by penicillin, we have had an opportunity of investigating the factors that prevented recovery and of assessing the extent to which healing had progressed during the interval of up to three months between arrest of the infection and death.

Successful Cases

The events during treatment in a typical successful case are illustrated in Fig. 2. The temperature fell to normal within a few days of beginning treatment but the pulse settled much less rapidly; usually the rate remained somewhat rapid for two to four weeks. In the case illustrated the patient was confined to bed for three weeks after the end of treatment although the temperature and pulse rate were normal; carefully graduated and cautiously applied bed exercises were then started but were followed by an immediate rise in the pulse rate and, when the patient was allowed up for a few minutes ten days later, the pulse rate increased to 116 a minute taking several weeks to return to normal. In this case the history of infection was comparatively short and the general condition of the patient good, but it is clear that the heart had been considerably damaged by the infection. Great care is necessary during the period of increasing activity following successful treatment, however well the patient may appear when resting in bed; similar opinions were expressed by Anderson and Keefer (1945) and Meads, Harris, and Finland (1945).

The first blood culture after beginning penicillin was made between the first and seventh days of treatment and was sterile in 16 of our 18 successful cases; in the remaining 2 blood cultures were positive on the second day but sterile on the ninth day of treatment. In successful cases, once the blood was rendered sterile, subsequent cultures were always negative during treatment, but 3 patients, who ultimately recovered, relapsed after the initial course of penicillin had been completed.

In 4 successful cases cardiograms before treatment showed very low voltage T waves in all the limb leads but subsequently returned to normal (Fig. 7). T wave changes associated with heart failure were noted by Bloomfield *et al.* (1945), but heart failure did not occur in our 4 cases.

During and after treatment the sedimentation rate fell slowly and, in our successful cases, reached normal in an average of five weeks after the completion of treatment.

There was often little rise in hæmoglobin during treatment but subsequently steady improvement took place and a normal level was attained, without transfusion, about three months after the end of treatment (Fig. 3). Transfusion was necessary in only two successful cases and is to be avoided if possible owing to its dangers when heart failure is present.

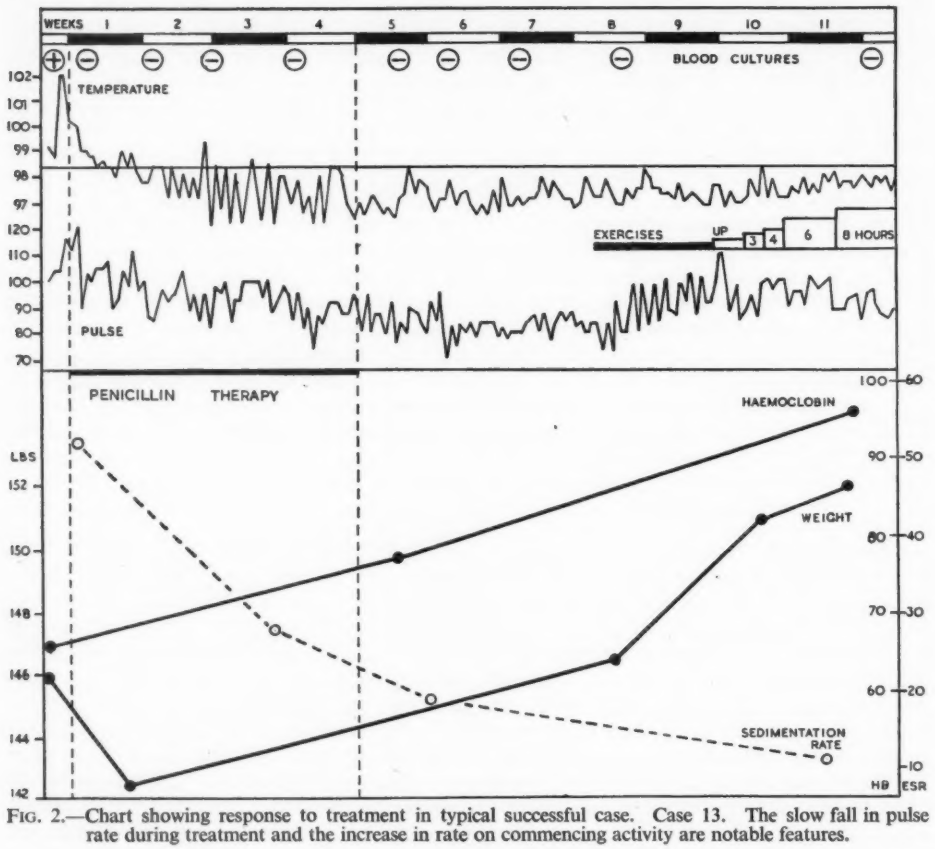


FIG. 2.—Chart showing response to treatment in typical successful case. Case 13. The slow fall in pulse rate during treatment and the increase in rate on commencing activity are notable features.

Gain in weight continued for up to nine months after treatment and in eight of the successful cases the gain averaged 23 lb.

The convalescence of these patients was, therefore, slow and, owing to the cardiac damage, required careful management. The average period in hospital was fourteen weeks in our successful cases; full activity was rarely resumed sooner than six months after the end of treatment.

Degree of Recovery

A severe infection of the myocardium and valves leading to tissue destruction and fibrosis, present for periods up to six months before arrest by penicillin, is likely to leave behind it

further cardiac damage. We have tried to assess the frequency and severity of this damage in three ways: (1) by comparing the patients' capacity for effort and ability to follow their occupation before infection and after recovery, (2) by reviewing the radioscopic changes in the size and shape of the heart and the changes in the cardiogram during the recovery stage, and (3) by searching for physical signs indicating new valvular lesions or increase in the severity of established lesions.

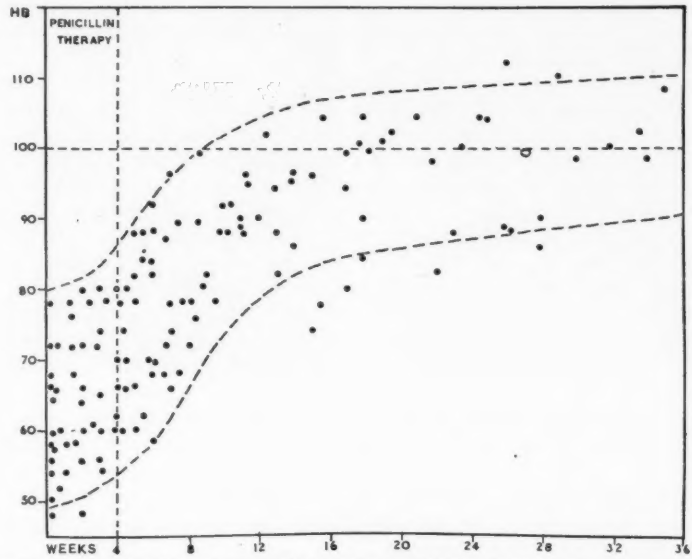


FIG. 3.—Scatter graph showing rise in hæmoglobin without transfusion in 12 successful cases with an initial hæmoglobin below 80 per cent.

The previous occupations of 18 recovering patients and the number who have, so far, returned to work are enumerated in Table VI. Of our 18 patients, 12 are back at their old work and all say that they notice no change in their capacity for exertion. One of these, who gave up her work as a machinist on marriage, has resumed her employment although she now has a young child born during the infection. Following that confinement she was given a ten-day course of treatment, but subsequently relapsed and, during her second course of penicillin, developed a coronary embolus with cardiographic changes indicating posterior infarction.

TABLE VI

RETURN TO WORK OF 18 RECOVERING PATIENTS

Categories	Before infection	After treatment	
		Number resuming old work	Number not resuming old work
In employment	10	6	4
Housework	7	6	1
At school	1	—	1
Totals	18	12	6

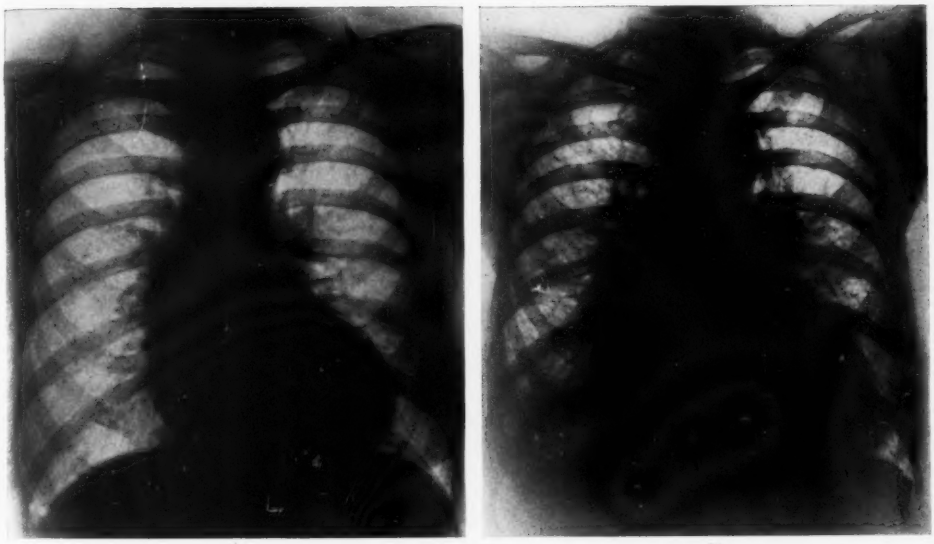
One of the 6 patients who have not resumed work is still convalescent (33), one is fit for work and maintains that he is as well as before his illness but he has a specialized occupation and has not yet found suitable work. One patient had considerable restriction of her capacity for effort (Class III) before the infection; she seems no worse now but has been advised not to resume work as there is no economic necessity for her to do so. Three patients have subjectively deteriorated (10, 17, 22), and are unfit for work.

The degree of recovery in these cases is surprisingly good; unfortunately, subjective estimation of fitness by the patient is open to error and objective methods reveal another aspect of the picture.

Teleradiograms and Cardiograms. It is difficult to obtain strictly comparable teleradiograms for the serial measurement of heart size; we have, therefore, disregarded small changes in the cardiothoracic ratio that could be explained by a difference in position of the chest or diaphragm and have confined our attention to undoubted alterations in size.

In untreated subacute bacterial endocarditis the size of the heart increases progressively as the disease advances for, in 6 of our cases, comparison of teleradiograms taken earlier in the illness with those before treatment showed that in each case the heart had increased in size, sometimes considerably (Fig. 4). After treatment there was no further increase in heart size in 13 of the 16 successful cases in which we have adequate serial teleradiograms. This suggests that, as we should expect, cardiac damage due to the infection does not often increase after successful treatment. But we have little evidence to indicate that the enlargement which occurs during the infection diminishes appreciably after apparent cure of the disease; in 9 of our 13 cases the heart size has remained unchanged for periods between six and eighteen months after treatment, and in only 4 cases has there been any suggestion of a decrease in size. In 1 of these 4, this decrease followed ligation of a patent ductus (Case 33) and is, therefore, irrelevant to this discussion; in the other 3 we are not convinced that the alteration is sufficient to be significant. Our observations, therefore, indicate that after successful treatment the progressive cardiac enlargement of the untreated disease usually stops, but enlargement that has already taken place is generally irreversible.

In 3 patients cardiac enlargement continued after treatment; all these are less fit than before the infection. Case 10 is interesting for she first came under our observation when pregnant, four weeks before the first symptom of infection. She then had a loud aortic diastolic murmur, maximal to the left of the sternum and audible at the apex, with a soft systolic murmur maximal at the apex but no clear evidence of a mitral lesion. The blood pressure was 150/45. The infection was treated six weeks after the first symptom appeared and the physical signs remained unchanged. A year later a rough aortic systolic murmur and thrill appeared, but the aortic lesion remained predominantly regurgitant for the blood pressure was 135/35. Three months later a rumbling mitral diastolic murmur was heard for the first time and cardioscopy revealed increased prominence of the pulmonary conus (Fig. 5) but, although the change in the valvular lesions is clinically obvious, the cardiac silhouette is not yet grossly modified and there is no significant alteration in the cardiogram. The other two cases form a striking contrast for, although the physical signs have altered much less, the heart has considerably enlarged since treatment and serial cardiograms have shown significant changes. In Case 22 the progressive increase is illustrated in Fig. 6 and the development of right axis deviation in Fig. 7 (A and B). No diastolic murmur has been heard at any stage, but the apical systolic murmur is now louder. In Case 17 progressive cardiac enlargement followed the completion of treatment (Fig. 8) and comparison of the cardiogram taken before treatment with that a year later showed that, in addition to recovery of the T waves previously noted, the P waves had changed and the electrical axis had shifted towards the right (Fig. 7). Although the radiograms are typical of advanced mitral stenosis there has never been a diastolic or presystolic murmur, but the apical systolic murmur has become much louder. In these

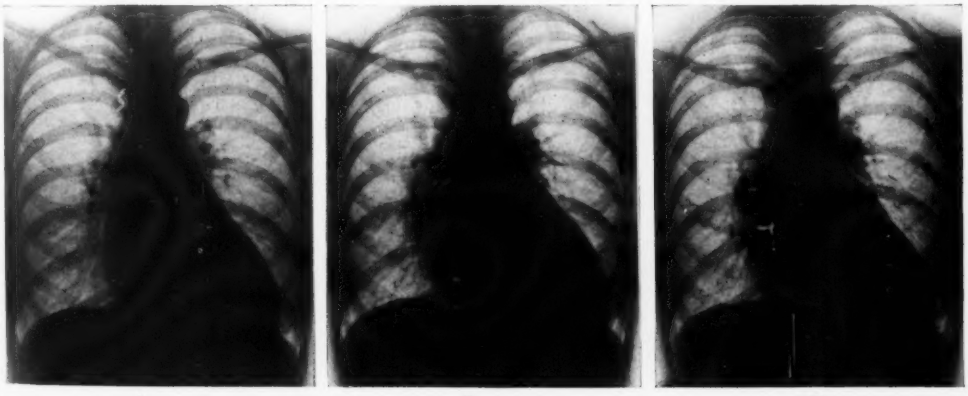


A B

FIG. 4.—Teleradiograms showing cardiac enlargement in untreated subacute bacterial endocarditis. Case 8. (A) Six weeks before treatment. (B) Three days before treatment. A considerable change has occurred in a few weeks.

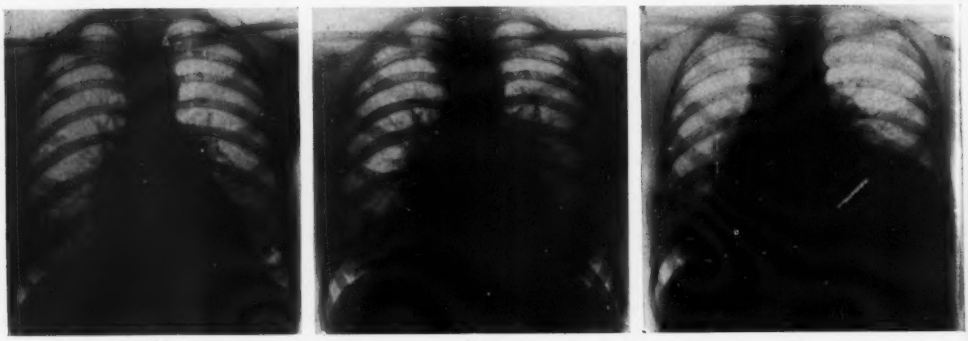
two cases it is difficult to account for the enlargement of the right ventricle and the changes in axis deviation except by the development of increased mitral stenosis.

These three cases suggest the possibility that stenotic valvular lesions may occasionally develop or increase after successful treatment with penicillin; this is not unlikely since repair



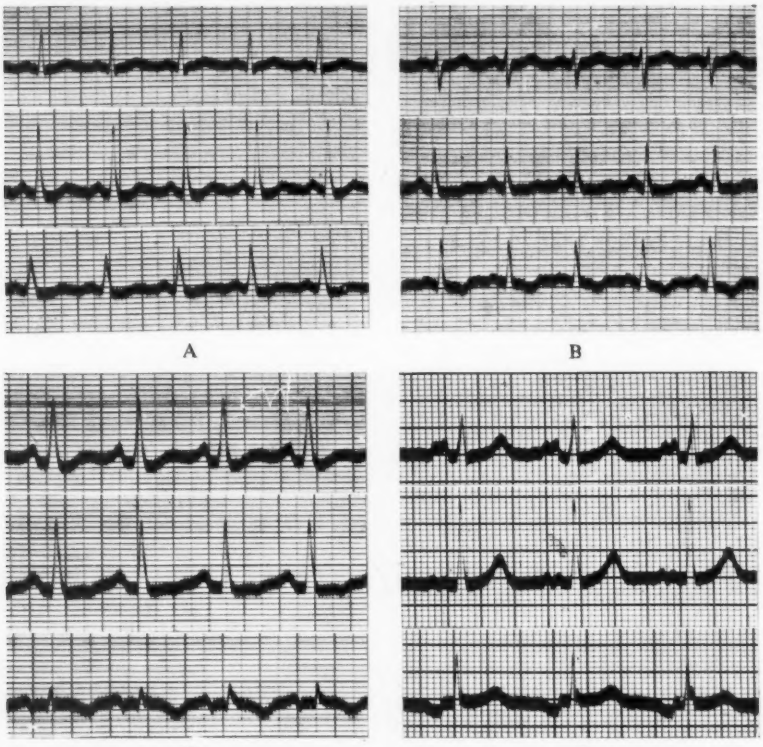
A B C

FIG. 5.—Teleradiograms. Case 10. (A) Before treatment. (B) Twelve months after treatment (C) Seventeen months after treatment, showing slight prominence of pulmonary conus.



A B C

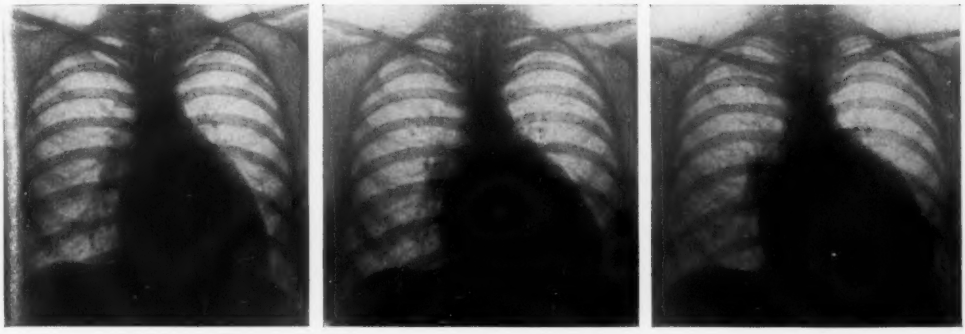
FIG. 6.—Teleradiograms showing progressive cardiac enlargement after control of infection. Case 22 (A) Before treatment. (B) Two months after treatment. (C) Nine months after treatment, showing gross enlargement. (See cardiograms, Fig. 7.)



A B C D

FIG. 7.—Cardiograms. (A) Case 22, during treatment. (B) Case 22, three months after treatment, showing development of right axis deviation. (C) Case 17, during treatment. (D) Case 17, one year after treatment, showing recovery of T waves, change in form of P waves and increase in voltage of QRS III with decrease in voltage of QRS I, indicating a shift of the electrical axis towards the right. (Reduced to four-fifths.)

of the valvular damage is accompanied by fibrosis. If the infection largely destroys the valve, a stenotic lesion is most unlikely to develop during healing; it is the less damaged valve which will be liable to this complication. We cannot, of course, be sure that the changes are not due to the spontaneous progress of the rheumatic lesions but it is doubtful if this explanation is adequate.



A B C

FIG. 8.—Teleradiograms showing progressive cardiac enlargement after control of infection. Case 17. (A) Three days after treatment. (B) Four months after treatment. (C) Ten months after treatment. (See cardiograms, Fig. 7.)

Relapses

In 5 cases short courses of penicillin had been given before admission; a positive blood culture was subsequently obtained in all. In 3 the relapse occurred within two weeks and in the others at some unknown period within five weeks and four months respectively. It appears that when the relapse was promptly detected and adequate treatment instituted, recovery followed, but, in both cases in which there was delay in detecting the relapse the patient died.

TABLE VII

RELAPSES FOLLOWING INITIAL COURSE AFTER ADMISSION

Case	Course	Time of relapse after end of course	Subsequent treatment	Result
1	1×5	0–5 days	¼×18	Died
2	1×10	9–13 weeks	½×28	Well
3	½×10	21 days*	½×28	Well
4	½×10	0–9 days	½×9	Well
12†	½×22	0–6 days	½×20	Died

* No culture, recurrence of pyrexia.
† Insensitive organism, died during second course.

In 5 cases a relapse followed the initial course after admission (Table VII) in 3 cases within a week of the end of treatment, and in 1 case three weeks after treatment. The remaining case is interesting; thirteen weeks after a short course of treatment a positive culture was obtained although the patient was free from symptoms and there were no clinical signs of infection. Regular blood cultures are, therefore, necessary during convalescence for early detection of relapses which may not, at first, show much clinical deterioration. Two patients

whose infection relapsed following inadequate treatment after admission ultimately died, one was infected with an insensitive organism and the other, our first case, never had a full course of penicillin.

Relapses following inadequate treatment, if promptly detected and adequately re-treated, do not appear to have prejudiced the ultimate outcome in these cases. In their case Florey and Florey (1944) found a four-fold increase in the resistance of the organism after treatment; they attributed this to penicillin therapy. Bloomfield and Halpern (1945) also found one case in which an organism, sensitive before treatment, became insensitive after treatment, and Christie (1946) considers that, in assessing the danger of inadequate treatment, this possibility ought not to be ignored. In one of our cases, in which the blood culture remained positive during treatment, the resistance of the organism increased from 4 to 18 times that of the Oxford staphylococcus. On the other hand, Meads *et al.* (1945), Anderson and Keefer (1945), and Dawson and Hunter (1946) were unable to find any change in the resistance of the causative organisms in their cases. Since the measurement of resistance is open to criticism, the response to re-treatment may be a more reliable test; there is at present no evidence to suggest that if patients infected with an initially sensitive organism relapse after inadequate therapy, they will often fail to respond to a subsequent full course. Relapse after prolonged treatment may carry a graver prognosis as Christie (1946) has suggested. No patient in this series relapsed after a 28-day course but, from our subsequent experience, we know this can happen even if the organism is sensitive.

Unsuccessful Cases

It is essential to know how often death is due to failure to control the infection. We have studied this problem in three ways: (1) by clinical assessment of the control of infection, (2) by histological assessment of the degree of healing, and (3) by post-mortem culture of the vegetations.

Clinical Criteria of Control of Infection. In successful cases the blood culture became negative and the temperature fell to normal by the end of the first week. Recurrence of pyrexia in the second week was not regarded as significant if the blood culture remained sterile. Usually there was little rise in hæmoglobin or gain in weight during treatment. After successful penicillin treatment the weekly blood culture remained sterile and the temperature was normal unless another infection was present or major infarction took place; the hæmoglobin and weight increased steadily.

Histological Criteria of Healing. In untreated subacute bacterial endocarditis the vegetation consists essentially of a thrombus lying on a valve and covered, wholly or in part, by a layer of organisms. Organization is present, for fibroblasts and capillaries grow into the thrombus from the valve and are associated with large mononuclear cells. Polymorphs, and frequently lymphocytes, indicate active inflammation at the base of the vegetation and in the adjacent valve.

After penicillin therapy the first sign of healing was the disappearance of the active inflammatory lesion; removal of the hyaline thrombus by mononuclear cells then began and foreign-body giant cells appeared in the zone of bacteria. Although organisms were still present at this stage, they stained less readily and were presumably dead since cultures from the vegetation remained sterile. Finally, in the most advanced stage of healing that was seen, the thrombus was very small, often consisting of a little hyaline material lying on scanty fibrous tissue but sometimes calcified, when rather more fibrous tissue was found.

The degree of healing was assessed solely on histological grounds, without reference to clinical evidence of control of infection or period of survival after the completion of treatment. The vegetations were classified, according to the degree of healing, into three stages (Table VIII).

TABLE VIII

HISTOLOGICAL CRITERIA OF HEALING

Stage 1.—Indistinguishable from vegetations of untreated case—active inflammation.
Stage 2.—Much organization, no inflammatory reaction (or only slight): intermediate between Stages 1 and 3.
Stage 3.—Organization advanced, probably nearly healed.

Feature	Stage 1	Stage 2	Stage 3
Polymorphs in vegetation or valve	Moderate number	Few or none	None
Mononuclear cells in vegetation	Some	Some	Few or none
Growth of endothelial cells over vegetation ..	Never	Never	Often
Newly formed fibrous tissue	Little	Much (cellular)	Variable amount
Organisms	Yes	Yes	Sometimes
Positive culture from vegetation	Sometimes	Never	Never

In untreated bacterial endocarditis, although acute inflammatory changes are always present in some part of the lesion, there may also be areas of healing; in assessing healing in these cases it was, therefore, necessary to examine several sections from each vegetation and to form an opinion from the composite picture. A general impression of the process of healing after penicillin therapy can be gained from the naked-eye appearances and these are illustrated in Fig. 9.

Post-mortem Culture of Vegetations. Before removal of the heart all the great vessels were tied; the heart was then removed intact. With aseptic precautions the ventricular wall

TABLE IX

CONTROL OF INFECTION AND DEGREE OF HEALING IN 15 FATAL CASES

Case	Time of death	Duration of normal temperature before death	Duration of sterile blood culture before death	Anatomical condition of vegetations *	Post-mortem culture of vegetations	Control of infection	Degree of healing
	During treatment						
5	6th day	2 days	—	—	—	?	—
20	6th day	3 days	2 days	Stage 1	Strept. viridans	0	0
9	15th day	nil	nil	(*a*) Stage 1; (*b*) Stage 2	—	0	±
12	20th day†	7 days	5 days	Stage 1	Sterile	?	0
25	20th day	5 days‡	14 days	Stage 1	Sterile	+	0
23	27th day	nil	nil	(*a*) and (*b*) Stage 1	B. coli only§	0	0
30	27th day	24 days	24 days	(*a*) and (*b*) Stage 1	Sterile	+	0
	After treatment						
28	4 days	10 days‡	26 days	(*a*) and (*b*) Stage 2	Sterile	+	+
8	4 weeks	7 weeks	8 weeks	—	—	+	−
29	4 weeks	nil	8 weeks	Stage 2	Sterile	+	+
1	6 weeks	nil¶	8 weeks	(*a*) Stage 2; (*b*) Stage 3	Sterile	+	++
14	10 weeks	13 weeks	13 weeks	Stage 2	Sterile	+	+
26	10 weeks	10 weeks‡	13 weeks	—	—	+	−
6	13 weeks	16 weeks	17 weeks	Stage 2; (*a*) and (*b*)	—	+	++
7	13 weeks	16 weeks	17 weeks	(*a*) and (*b*) Stage 3	—	+	+++

* When more than one valve was affected the degree of healing is stated in both.
† Two courses of treatment.
‡ Penicillin pyrexia.
§ B. coli septicæmia during life.
‖ B. coli urinary infection.
¶ Multiple pulmonary emboli after treatment.

was incised, portions of the vegetations removed, ground up in a sterile mortar, and inoculated on to blood agar plates and into Hartley broth.

The observations made in these three ways in 15 fatal cases are summarized in Table IX. In Cases 5 and 20, death occurred too soon after beginning treatment to estimate the full effect of penicillin but the temperature had been rapidly controlled in both. In Case 20, however,

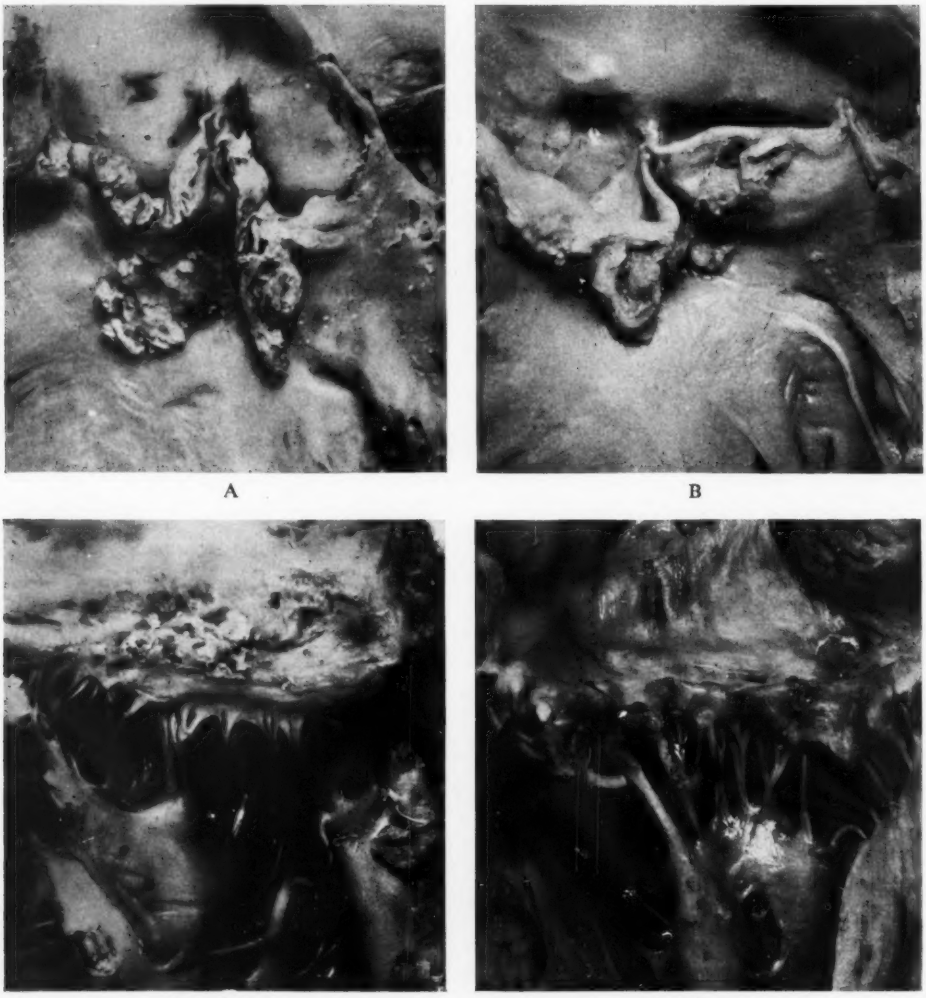


FIG. 9.—Healing of vegetations after treatment. (A) Case 9, aortic valve. Death on fifteenth day of treatment; histologically indistinguishable from untreated case (Stage 1). (B) Case 28, aortic valve. Death four days after treatment; vegetations histologically healing (Stage 2). (C) Case 9, mitral valve. Vegetations histologically healing (Stage 2). Compare with unhealed lesion on aortic valve of same case (A). (D) Case 7, mitral valve. Death thirteen weeks after completion of treatment. Vegetations almost completely healed histologically (Stage 3).

in spite of the sterile blood culture during life, *Strept. viridans* was isolated from the vegetations after death. This type of case, in which a sterile blood culture can be obtained although living organisms are present in the vegetations, has been previously described by Meads *et al.* (1945); it probably represents an early stage in the response to penicillin and may explain the need to continue treatment long after the blood is sterile.

In Cases 9, 12, and 23, we cannot regard the infection as controlled, but there was some response to treatment in Case 12; this supports the suggestion recently made by Gordon and Zinnemann (1945) that some strains of *Hæmophilus influenzæ* are sensitive *in vitro* to high concentrations of penicillin. In the other two dying during treatment (Cases 25 and 30) the infection appeared clinically controlled and the vegetations were sterile at necropsy, but there was no histological evidence of healing.

Eight cases died after treatment; in all the infection had been clinically controlled and cultures of the vegetations, made in four, were sterile. Evidence of healing was present in all the six examined histologically, and was more advanced in those who lived longest after treatment.

Thus, of 13 cases dying after the first week of treatment, there is evidence of failure to control the infection in only 3; one of these showed some response clinically, and none completed a full course before death. Histological evidence of healing was not present until some time after clinical control of infection and sterilization of the valves, and did not reach an advanced stage until the infection had been clinically controlled for three months.

Causes of Death

Since in most of our cases death cannot be attributed directly to the infection, other adequate causes of death should be demonstrable and this proved to be so: heart failure, uræmia, or vascular accidents were the usual immediate causes (Fig. 10). In Table X the clinical causes of death are compared with the post-mortem findings in 13 cases. Infection was a direct cause of death only when the patient died during treatment and major embolic

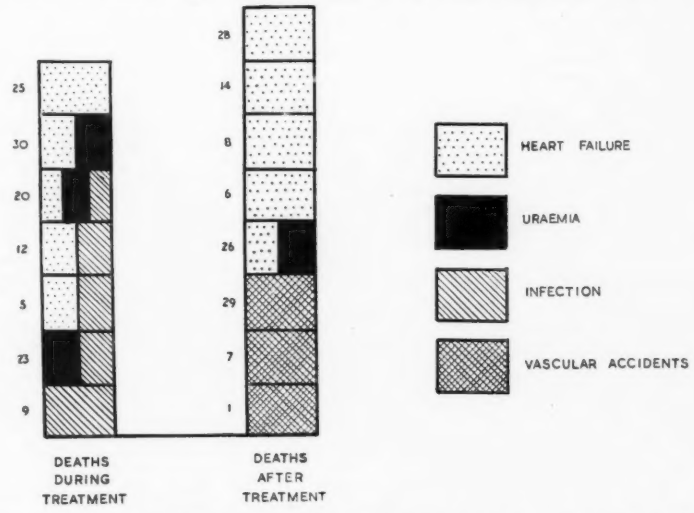


FIG. 10.—Diagram showing clinical causes of death in 15 cases. When more than one factor appeared important, all have been represented.

accidents led to death only in those surviving treatment. Heart failure and uræmia occurred in both groups.

Heart failure was the most important cause of death for of 18 cases without failure only 2 died, whereas of 15 with failure 13 died; in 5 of these heart failure was the sole cause of death, in 5 it was a major factor, but in 3 failure was not severe when death occurred from other causes.

TABLE X

CAUSES OF DEATH

Case	Time of death	Clinical cause of death	Principal post-mortem findings
	During treatment		
5	6th day	1. Left heart failure. 2. ? Infection.	1. Pulmonary œdema. 2. Active myocarditis. 3. Hypertrophy and dilatation of left ventricle. 4. Nephritis.
20	6th day	1. Uræmia. 2. Right heart failure. 3. ? Infection.	1. Nephritis. 2. Congestive (systemic) heart failure.
9	15th day	Infection.	1. Pulmonary œdema (slight). 2. Active myocarditis. 3. Hypertrophy and dilatation of left ventricle.
12	20th day	1. Acute left heart failure. 2. ? Infection.	1. Pulmonary œdema (much) and congestion. 2. Nephritis.
25	20th day	Left heart failure leading to right.	Congestive (systemic) heart failure.
23	27th day	1. Uræmia. 2. Infection.	Pyelonephritis.
30	27th day	1. Uræmia. 2. Right heart failure.	1. Nephritis. 2. Congestive (systemic) heart failure. 3. Bronchopneumonia.
	After treatment		
28	4 days	Acute left heart failure.	1. Pulmonary œdema (moderate) and congestion. 2. Active myocarditis. 3. Hypertrophy and dilatation of left ventricle.
8	4 weeks	Left heart failure leading to right.	No necropsy.
29	4 weeks	Cerebral hæmorrhage	Cerebral hæmorrhage.
1	6 weeks	Pulmonary infarction.	Pulmonary infarction.
14	10 weeks	Left heart failure leading to right.	1. Congestive (systemic) heart failure. 2. Pulmonary œdema (slight) and congestion. 3. Peritonitis.
26	10 weeks	1. Uræmia. 2. Left heart failure leading to right. 3. Acute hepatitis.	No necropsy.
6	13 weeks	Left heart failure leading to right.	1. Congestive (systemic) heart failure. 2. Bronchopneumonia.
7	13 weeks	1. Cerebral hæmorrhage. 2. Pulmonary embolism from femoral venous thrombosis.	1. Cerebral hæmorrhage. 2. Pulmonary embolism and femoral venous thrombosis.

Heart failure usually developed when considerable cardiac enlargement was present (Table XI) and it is interesting to consider the factors upon which the size of the heart depended. The size before infection is naturally a factor but, unfortunately, we generally have no record of this. As we have shown, the progress of the infection leads to a progressive increase in the heart size in all those where we have data bearing on the point. It is, therefore, to be expected that the longer the infection has been present the larger the heart will be; on comparing the heart size before treatment with the duration of the illness (Table XI) it was found that of 7 patients with car diohoracic ratios of 1·5 or less, 6 had suffered from symptoms of infection for fifteen or more weeks and 6 had heart failure, whereas of 8 without cardiac enlargement, only 1 had been ill for more than fifteen weeks. This direct relation between the dura-

tion of the bacterial endocarditis and the heart size suggests that cardiac damage owing to the infection plays an important part in producing cardiac enlargement and heart failure.

Myocardial lesions and valvular damage may both be important in the production of cardiac enlargement and heart failure in untreated bacterial endocarditis. The inflammatory and embolic myocardial lesions have been studied in the untreated disease by Bracht and Wachter (1909), Saphir (1935), and De Navasquez (1939). Small coronary emboli, structurally similar to the vegetations, appear to be common histologically; De Navasquez (1939) demonstrated such lesions in 16 of his 20 untreated cases. The lesions studied by Bracht and Wachter (1909) led to destruction of muscle tissue and some healing took place in the untreated disease.

TABLE XI

COMPARISON OF HEART SIZE, INCIDENCE OF HEART FAILURE, DEATH, AND DURATION OF INFECTION

Cardiothoracic ratios	Number of cases	Number with heart failure	Number of deaths from heart failure	Number with symptoms of infection for 15 or more weeks
2·0 or more	8	1	0	1
1·9 or 1·8	7	1	1	2
1·7 or 1·6	6	4	2	3
1·5 or less	7	6	6	6
Totals	28*	12	9	12

* Five cases, unfit for cardioscopy, omitted.

The histology of the myocardium has been examined in 13 of our cases; our examination was not exhaustive for routine sections were taken only from a standard site in the ventricular septum though sometimes additional sections from other parts of the myocardium were examined. Fibrotic and inflammatory lesions were present in 9; these were severe in 5 cases. Libman and Friedberg (1942) were inclined to minimize the importance of myocardial lesions, but heart failure was a principal cause of death in 4 or our 5 cases with severe lesions whereas this was true of only half of those with slight lesions or no lesion. Although these figures are not incompatible with the contention of Buchbinder and Saphir (1939) that myocardial lesions play an important part in the production of heart failure, there can be little doubt that valvular damage is often more important as Bloomfield *et al.* (1945), Bloomfield and Halpern (1945), and Rosenblatt and Loewe (1945) found in their cases. In our Case 25 the blood pressure suddenly altered from 140/90 to 145/55 owing to rupture of an aortic cusp three days before treatment; this led to heart failure and a change in the cardiothoracic ratio from 1·8 to 1·4. Death occurred 23 days later and the valve perforation was confirmed at necropsy. Since the infection frequently attacks the aortic valve, failure will often be associated with aortic incompetence, as Mokotoff *et al.* (1946) showed. Of our 29 cases with rheumatic heart disease, 16 had aortic incompetence on admission and 10 of these developed failure; 2 others developed aortic incompetence under our observation and failure followed in both, whereas heart failure occurred in only 2 of 11 without aortic incompetence. If damage to the aortic valve by the infection is an important cause of failure, we should expect left heart failure to be common. Excluding one case in which failure was associated with a congenital lesion, left heart failure was present in 10 of our cases and was followed by right heart failure in 6; 9 of these had aortic incompetence. In 3 right heart failure was present on admission; all 3 had aortic incompetence and we cannot be certain that left heart failure had not been

present in the earlier stages, but there was no history of paroxysmal dyspnœa. In the remaining case right heart failure developed during treatment.

In short, heart failure was present in nearly half and was a principal cause of death in two-thirds of those that were fatal. Recovery was uncommon in those with failure and the rule in those without it. Heart failure occurred principally after long-standing infection and was generally associated with much cardiac enlargement and aortic incompetence; it was usually left-sided at the onset. Both myocardial and valvular damage due to the infection were probably factors in producing failure but the valvular lesions played the more important part. As most of our patients had only slight cardiac lesions before the infection, we consider that the cardiac damage due to the infection played a more important part than the underlying congenital or rheumatic lesion in causing failure. Since the infection usually attacks the aortic valve, the frequency of left heart failure and its association with aortic incompetence support this contention.

Renal Damage. Impairment of renal function was found clinically in 10 cases; in one other no renal function tests were made before death on the sixth day of treatment but at necropsy a severe nephritis was present. Renal impairment never appeared for the first time during or after treatment. As Levy and McKrill (1946) found, the longer the duration of infection the greater the proportion of patients with severe renal damage (Table XII).

TABLE XII

COMPARISON OF DURATION OF SYMPTOMS WITH RENAL IMPAIRMENT AND WITH NUMBER OF DEATHS

Duration of symptoms of infection	Number of cases	Number with impaired renal function	Number of deaths
Less than 10 weeks..	7	1	0
10–19 weeks..	13	4	4
20–29 weeks..	7	3	5
30 or more weeks	6	3	6

Of these 11 patients with severe renal damage only 2 recovered; in one case the standard urea clearance was 19 per cent on admission and the blood urea 104 mg. per 100 c.c.; during the third week of treatment the figures were 68 per cent and 48 mg. per 100 c.c. and two weeks after treatment the urea clearance was 96 per cent and the blood urea 34 mg. per 100 c.c. In the other case the initial urea clearance was 40 per cent and the blood urea 42 mg. per 100 c.c.; during treatment the blood urea rose to 64 mg. but eight weeks after treatment it was 26 mg. and the urea clearance 86 per cent. Renal function also improved in 2 of the 9 fatal cases; in 4 no serial data are available, and in 3 the renal impairment increased before death. Four died in uræmia with final blood urea levels of 484, 220, 152, and 148 mg. per 100 c.c.; additional possible causes of death were present in all (Fig. 10).

It was possible to study the renal histology in 11 of 15 fatal cases; the clinical and histological findings are summarized in Table XIII. In 4 of these 11 there was severe, and in 2 slight impairment of renal function before death, but none had hypertension during life. All the 4 with severe impairment of renal function had a severe nephritis histologically, as did one without renal function tests during life. In 4 cases this was a diffuse glomerular nephritis, 2 acute and 2 subacute, and in 1 pyelonephritis was found. In the 2 with slight impairment of renal function the only lesion was glomerular fibrosis not unlike that described by Bell (1932) in untreated subacute bacterial endocarditis; this was also present in 5 others and 2 of these were known to have no clinical impairment of renal function. In 2 there was increased intercapillary hyaline material similar to that found by Ellis (1942) in his Type II nephritis; neither had nitrogen retention during life. The typical focal glomerular necroses of embolic

nephritis were present in only 2 cases and these changes were limited to a few glomeruli. The renal histology thus showed a variety of changes and was characterized by the frequency of diffuse glomerular lesions, whereas focal embolic lesions were uncommon.

TABLE XIII

KIDNEYS—CLINICAL AND HISTOLOGICAL FINDINGS. (11 CASES)

Case number	5	6	7	9	12	20	23	25	28	29	30
Blood pressure	120/30	115/85	150/80	120/50	125/25	110/75	150/50	140/90	150/50	105/60	130(/0)
Urea clearance	—	83%	—	60%	30–75%	—	17%	89%	60%	—	60%–?
Blood urea	—	24	—	26	66–22	484	124–148	26	28	36	56–220
Gross abnormality urinary deposit	+			+	+	+	+			+	+
B. coli urinary infection	+	—	—	—	—	—	+	—	—	+	—
Acute diffuse glomerular nephritis	+										+
Subacute diffuse glomerular nephritis					+	+					
Pyelonephritis							+				
Glomerular fibrosis	+	+	+	+				+	+	+	
Increased intercapillary hyaline material		+								+	
Focal glomerular necrosis	+									+	

Libman and Friedberg (1942) described diffuse glomerular nephritis in untreated bacterial endocarditis and found it more frequently in the bacteria-free stage. They considered that it led to progressive renal impairment and death from uræmia in at least one-third of their cases dying in the bacteria-free stage and remarked on the absence of hypertension, unless present before the nephritis. Loewe and Rosenblatt (1945) recorded one case, unsuccessfully treated with penicillin, with diffuse glomerular nephritis but no focal glomerular lesions; the blood pressure was 120/80, and later 120/40.

Thus diffuse glomerular lesions, without hypertension, occur not infrequently in bacterial endocarditis. The presence of gross renal insufficiency in 2 of our recovering cases, and the improvement of renal function in 2 of our unsuccessful cases, suggests that similar types of renal damage may be compatible with recovery after penicillin therapy. If this is so, it is possible that when renal function is impaired during the active stage, progressive renal insufficiency may develop long after successful treatment; a long-term study of recovering cases with past renal impairment should decide this.

Major Embolic Accidents. There were 21 patients with major embolic accidents, 17 before treatment, 8 during treatment, and 4 after treatment; the sites of lodgement were pulmonary in 6, cerebral in 7, renal in 8, splenic in 7, retinal in 3, and coronary in 1 case. The smaller number of major emboli during treatment is of little significance since the period of treatment was short compared with the duration of infection before treatment, but it is clear that major emboli are rare after treatment; if we exclude the 3 with cerebral or subarachnoid hæmorrhage in which embolization may have occurred some time previously, major emboli occurred after treatment in only one, who were never fully treated (Case 1).

One of the cases with cerebral hæmorrhage is interesting. Following a cerebral embolus nine months before treatment, she developed a left-sided hemiparesis which almost completely recovered; three months after the end of treatment, while apparently well, she suddenly collapsed unconscious with a severe left hemiplegia; she died five days later. At necropsy, a cerebral hæmorrhage had largely destroyed the right lenticular nucleus and internal capsule. It seems likely that the cerebral embolus led either to a mycotic aneurysm or to an area of softening but, owing to the disorganization of the affected area at necropsy, we were unable to determine which of these had caused the hæmorrhage. Cerebral embolism, with apparent recovery, may thus lead to fatal cerebral hæmorrhage many months after the infection is controlled.

Major emboli may occur at any stage of the disease; 3 of the 31 major emboli marked the onset of symptoms of infection, 11 occurred in the first ten weeks of the illness, 9 in the second ten weeks, and 8 subsequently.

Special Types of Case

Associated with Pregnancy. In 7 of our 22 female cases the infection began during pregnancy (Table XIV); this is a remarkably large number for Page and Campbell (1939) were able to find records of only 15 cases of subacute bacterial endocarditis associated with pregnancy when they published their own 3 cases. In the first two diagnosis was delayed: one of these was moribund on admission and died six days later; in the other the infection was controlled but death occurred three months after treatment from cerebral hæmorrhage. The other five were treated early and did well in spite of major vascular accidents in two and heart failure in one. Six children are well but in one case a macerated fœtus was expelled a few days before the beginning of treatment.

TABLE XIV

Cases Associated with Pregnancy

Case	Age	Stage of pregnancy at onset	Time before treatment	Confinement	Child	Mother	Remarks
5	26	Term	28 weeks	Normal	Well	Died	Regarded as puerperal pyrexia.
7	23	Term	46 weeks	Normal	Well	Died	Regarded as puerperal pyrexia.
3	19	33 weeks	10 weeks	Normal	Well	Well	Coronary embolism during treatment.
10	22	20 weeks	6 weeks	Cæsarean section	Well	Well	Subarachnoid hæmorrhage at 34th week.
18	28	20 weeks	5 weeks	Forceps for 2nd stage delay	Well	Well	Blood culture: negative 24th week, positive 25th week.
27	23	32 weeks	11 weeks	Normal	Well	Well	Dental extraction 23rd week pregnancy.
31	29	23 weeks	5 weeks	Abortion 28 weeks	Macerated	Well	Admitted for heart failure; pyrexia; culture positive.

Thus, provided the infection is promptly detected and adequately treated, the prognosis is good for mother and child. As these patients are usually under supervision, owing to the association of heart disease with pregnancy, the opportunity for early diagnosis is not lacking. Since confinement may have to be undertaken during the difficult period of convalescence, when the heart is unfit to carry additional burdens, it may be advisable to eliminate the physical strain of labour by Cæsarean section, particularly if there is likely to be any obstetrical difficulty.

With Patency of the Ductus Arteriosus. One of our patients, a girl of 13, had a patent ductus arteriosus infected by a pneumococcus. She had suffered from lassitude and pyrexia for three months before admission, and was then emaciated, very toxæmic, and severely dyspnœic owing to multiple pulmonary infarcts. The infection was controlled by a 28-day course of penicillin and her general condition improved, but she developed a left pneumothorax (Fig. 11), possibly from rupture of a septic subpleural infarct. Her subsequent progress was satisfactory and four months after treatment the ductus was ligated by Mr. Graham Bryce. Penicillin cover was used and there were no post-operative complications. After operation the heart decreased in size (Fig. 11).

Ligation of the infected ductus has given surprisingly good results (Shapiro and Keys, 1943; Tubbs, 1944; Gilchrist, 1945) but the success of penicillin in controlling the infection makes it possible to treat the infection first and, when the condition of the patient has improved, to ligate the ductus. Vesell and Kross (1946) have reported a successful case in which the ductus was ligated six days before the end of a 30-day course of treatment. They suggest

immediate operation if the organism is insensitive or the duration of infection more than three months or the response to penicillin doubtful. We do not yet know how often penicillin will control infection in a patent ductus but the general condition of our patient on admission excluded chest surgery and the ultimate result justified the attempt to control the infection by penicillin before contemplating surgical ligation of the ductus. If the infection of the ductus can be arrested by penicillin, this will lead to such improvement that the risk of subsequent surgical intervention will be materially diminished. We, therefore, consider that this method of management should receive adequate trial.

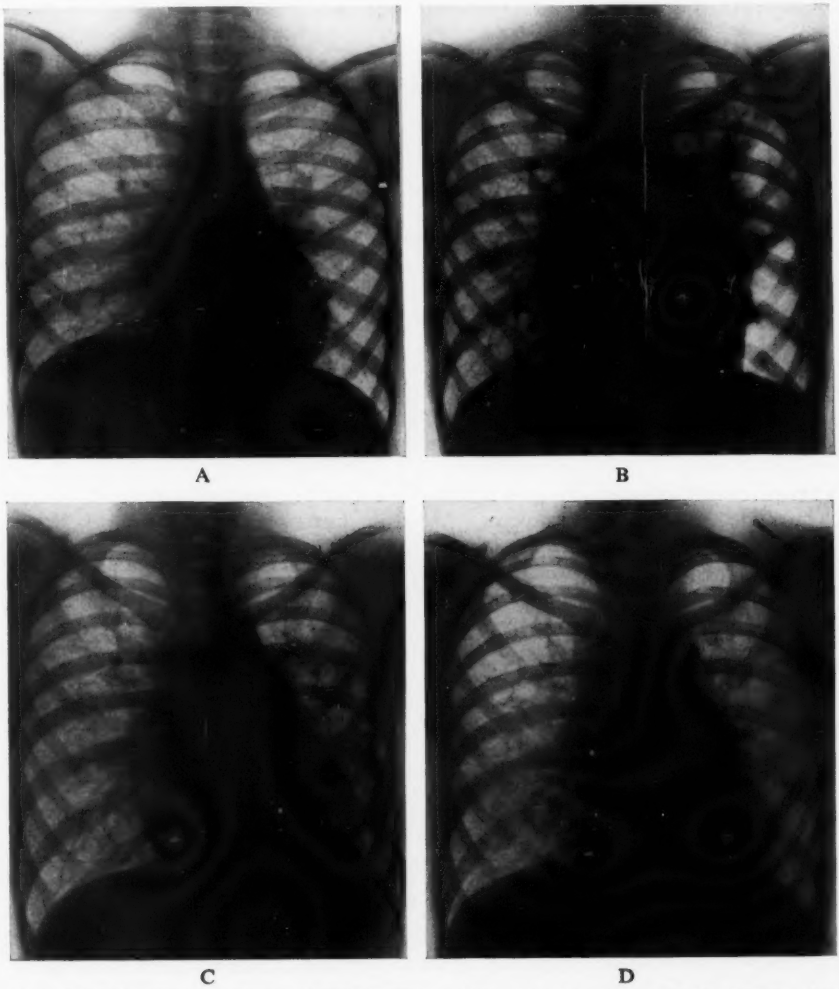


FIG. 11.—Infected patent ductus: Teleradiograms. Case 33. (A) Two months before treatment. (B) Fourth week of treatment, showing left pneumothorax and cardiac enlargement. (C) Three months after treatment and one month before ligation of ductus, showing absorption of pneumothorax but persistence of cardiac enlargement. (D) Two months after ligation of patent ductus, showing decrease of heart size.

Prognosis

Although failure to control the infection has rarely been a hindrance to success, yet nearly half our patients died. With such a means of arresting the disease in our hands we cannot be satisfied with this mortality and must seek to reduce it. Although we have studied only a small series, much evidence has been presented to indicate that the longer the duration of the infection the larger the heart, the more frequent renal impairment, and the more often do heart failure and uræmia prevent recovery. It is, therefore, to be expected that the mortality will be principally determined by the duration of infection; this has been illustrated in Table XII. When symptoms had been present before treatment for less than 10 weeks no patient died; none with symptoms for 30 or more weeks recovered and only two with symptoms for 20 or more weeks.

When we come to consider other factors it is more difficult to draw conclusions. It seems reasonable to suppose that the severity of cardiac damage before infection will play a part in leading to death when the additional burden of infection is added but, if we judge the severity of the underlying cardiac lesion from the patients' capacity for exertion before infection, no clear correlation with mortality emerges—6 of 17 cases in Class I died, 8 of 13 in Class II, and 1 of 3 in Class III. Unfortunately the last group with much reduced capacity for effort is too small to be useful, and the mortality may not be significantly higher in the intermediate group than in the apparently fit. Since the underlying heart disease was comparatively slight in most cases, it may be unimportant compared with the severe damage that may occur when the infection remains untreated for months.

In this series all patients over 50 years of age died, but there was no relation between age and mortality in the younger age groups. On comparing the number of deaths in each group with the duration of symptoms of infection it became clear that the mortality was determined by the duration of symptoms and not by the age. This is confirmed by the fact that two patients over 50 years of age, treated subsequent to this series, have both made good recoveries.

Factors such as the heart size (see Table XI) and the hæmoglobin level before treatment can be attributed to the infective process. When the hæmoglobin was over 70 per cent 2 of 9 cases died; when it was between 50–69, 9 of 16 cases died; and when it was under 50, 4 of 8 cases died. The degree of correlation between heart size on the hæmoglobin level and the mortality may be merely another indication of the severity and duration of infection.

TABLE XV

Comparison of Resistance and Number of Organisms with Number of Deaths

Resistance*	Number of cases	Number of deaths	Number of organisms per c.c. blood	Number of cases	Number of deaths
Less than 1	9	4	Less than 25.. ..	6	4
1–5	20	9	25–100	9	1
Over 5..	3	2	101–1000	9	5

* The resistance of the organism is expressed as a multiple of the resistance of the Oxford staphylococcus.

Provided the causative organism is sensitive to penicillin, neither the estimated degree of resistance to penicillin nor the number of organisms per c.c. of blood appear to be related to the mortality (Table XV). The importance of the resistance of the organism may be masked by the inaccuracy of the method of measurement, or the resistance may be truly unimportant up to a point, since the level of penicillin in the blood probably allows a safe margin unless the organism is insensitive.

With a much larger series it may prove justifiable to attach greater importance to some of these factors, but in our cases we are convinced of the importance of only one: the duration of the infection before treatment. This is, fortunately, a factor we can influence by early diagnosis and prompt treatment; if this can be achieved the present mortality should be materially reduced.

Failure of the patient to seek medical advice in the early stages is a most serious obstacle to the early diagnosis of some diseases, but this does not appear to be so in subacute bacterial endocarditis, for nearly three-quarters of our patients (24) were either under regular supervision for their heart disease at the onset of symptoms of infection, or sought medical advice when the first symptoms appeared. Of the other 9 only 4 delayed more than four weeks before seeking advice. The mortality is, therefore, closely related to the period under medical observation. If the disease had been suspected when these patients first sought advice, repeated blood culture by an adequate technique would have established the diagnosis, for, even with infections of short duration, we had no difficulty in isolating the organism. In these early cases non-specific symptoms predominate and signs are few; if penicillin treatment is to be successful the diagnosis must be suspected before the classical physical signs appear, for they indicate that the disease is well advanced and should serve as a warning that arrest of the infection may not avert death from heart failure or uræmia.

Summary

The treatment of subacute bacterial endocarditis by penicillin is described in 33 unselected cases with 15 deaths; the minimum period of observation after the completion of treatment was six months.

The clinical features of these cases, the methods of investigation, and the technique of laboratory procedures are described.

The clinical response to adequate treatment is described and the importance of careful management during convalescence is emphasized.

The degree of recovery is assessed in 18 successful cases; although most patients resume their old occupations, increased residual cardiac damage is the rule and a small proportion may develop stenotic valvular lesions during healing.

Relapses following inadequate therapy, if promptly detected and adequately treated, do not appear to prejudice the ultimate outcome.

The clinical and pathological evidence indicating control of the infection in unsuccessful cases is assessed; it is concluded that the infection was controlled in all cases completing treatment.

The process of healing is studied histologically in 12 cases: healing is not advanced until three months after clinical control of the infection.

The causes of death in 15 cases are discussed with a description of the post-mortem findings in 13 cases. The importance of heart failure in causing death is emphasized. Cardiac damage by the infection is the important cause of failure.

The renal lesions are studied histologically in 11 cases: diffuse, not focal, glomerular lesions predominate; and it is concluded that, if similar lesions occur in successful cases, they may lead to future renal insufficiency.

Seven cases associated with pregnancy are recorded; 5 mothers and 6 children survived.

In one case with an infected patent ductus arteriosus the ductus was ligated four months after successful penicillin treatment.

The factors that may have played a part in the outcome of treatment are discussed; evidence

is presented indicating that the duration of the infection before treatment is of the greatest importance. Reduction of the present mortality will, therefore, be most readily achieved by earlier diagnosis and treatment.

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INFECTIVE ENDOCARDITIS OF THE TRICUSPID VALVE

REPORT OF A CASE DUE TO STREPTOCOCCUS VIRIDANS

BY

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Post-mortem evidence shows that tricuspid lesions are more common than is generally supposed, though they often escape clinical recognition. Gilchrist and Lyon (1933) found that 10 per cent of 109 cases with mitral stenosis had tricuspid stenosis; and Coombs (1924) found that about one-third of all cases of rheumatic endocarditis had tricuspid involvement. That this lesion should pass undiagnosed during life is not surprising, for the physical signs are less constant.

Endocarditis lenta *per se* is unfortunately a common enough condition, but it affects in the main the left side of the heart. Though a fair number of cases of tricuspid endocarditis due to various organisms, such as gonococcus and pneumococcus, have been reported, comparatively few were due to *Strept. viridans*. Boldero and Bedford (1924), though they stress the frequency of infective endocarditis and congenital abnormalities, do not mention one case of tricuspid endocarditis in a series of 602 that they collected from various authors, and also confirm the relative infrequency of infective endocarditis of the right heart, mentioning only 30 cases affecting the pulmonary valves, that is 5 per cent. Hentel (1942) mentions one case; Marques *et al.* (1941) another, a patient with congenital tricuspid stenosis and auricular fibrillation, who developed infective endocarditis as a terminal event; and Hacker (1931) a third with a ruptured spleen and a subcapsular hæmatoma. Melnick *et al.* (1935) and Oerting (1931) also cite cases—the latter in a male, aged 46, where no blood culture had been done, but the diagnosis was confirmed post-mortem. Horder (1908) in a series of 118 post-mortem examinations, in a total number of 150 cases, mentions 14 with tricuspid involvement, together with mitral and aortic infection or both: no case of tricuspid disease occurred alone and the infection was generally pneumococcal.

Case Record

A male, aged 50 years, married and a shopkeeper by trade, consulted his doctor three weeks before admission to hospital, with a history of constant cough for seven days, which confined him to bed. On examination then, he had signs of pneumonia, temperature 102, respiration 36, pulse 120, but very few physical signs. He complained of pain in the right shoulder and chest midway in front. On exhibition of sulphapyridine, the temperature fell to normal in seven days; the pulse remained at 100, but rose two days later in spite of further sulphathiazole. The temperature continued to rise to 103° F., the urine contained albumin, and as the temperature would not settle, he was advised to go into hospital. His previous history and family history were not pertinent.

On admission, 8/4/43, he was seen to be a thin frail man of pale colour, temperature 100, pulse 98, respiration 24. The tongue was a fiery red with some furring. The teeth were very foul. There were no signs in any system, except some impaired resonance over the right basal region with diminished breath sounds and crepitations. The blood pressure was 138/90 and a white blood count was 8850 with 55 per cent neutrophils and 32 per cent

ymphocytes. A radiogram of the chest showed doubtful unresolved pneumonia in the right upper zone.

He was put on sulphamethazine, 4 g. to start with and 2 g. every six hours. Two days later his temperature had fallen and he felt slightly better. The sulphamethazine was stopped after a total of 26 g. had been given. On 12/4/43, his temperature began to swing upwards again. The chest showed crepitations in both mid-zones, without localizing signs, but it was thought that a lung abscess might be present. On 14/4/43, the total white cells rose to 11,050 of which 89 per cent were neutrophils. Another radiogram of the chest showed doubtful tuberculosis in the right mid-zone, but the sputum contained no acid-fast bacilli. A course of sulphadiazine was started on the 16th, but soon given up as there was no response. There were still no localizing signs but pallor and a polymorphonuclear leucocytosis persisted; no spleen was felt, but a blood culture and Widal were done and both were negative to abortus and the coli-typhoid group. On the 21st the right lung was explored but no pus was found and blood from the lung was sterile on culture.

On the 25th, he was transfused with one pint of blood, and on the 26th with a further pint; he was started again on sulphathiazole, to a total of 32 g., and this seemed to bring the temperature down. Petechiae appeared on the trunk, and on the 30th, systolic and diastolic murmurs were audible at the lower end of the sternum. An infective endocarditis was considered and blood culture which was repeated now grew a pure growth of *Strept. viridans*. On May 4th, a systolic murmur appeared at the aortic area. On the 7th, the systolic bruit at the base of the sternum was much louder, and suggested tricuspid endocarditis. On the 9th the patient became semi-comatose and died.

Post-mortem examination (Dr. Johns). Generalized petechial rash over body and limbs.

Chest. Right lung, adherent; left, free. Some congestion with early hypostatic pneumonia.

Heart. Gross pericarditis with early pus formation in the pericardial sac. A large mass of rough soft friable vegetations on the posterior cusp of the aortic valve. A smaller, harder, not so friable mass situated on a cusp of the tricuspid valve. No other abnormality of mitral or pulmonary valves. Heart muscle soft and friable. Coronary arteries patent. No gross atheroma. No emboli or thrombosis in great vessels. No sign of chronic rheumatism.

Abdomen. Solid organ congestion. Intestine showed petechial hæmorrhages. No emboli or aneurysm seen.

Brain. Some pus in basal cisterns, which on staining showed streptococci in fair numbers.

Diagnosis. Subacute bacterial endocarditis with pericarditis and terminal meningitis.

Discussion

This case is interesting from several aspects. The left heart is more frequently injured in endocarditis lenta, except in pneumococcal cases when according to Preble (1904), the relative frequency of right-sided involvement is greater than in acute endocarditis in general. Both sides were involved in this case. Allen (1935) suggests that in cases affecting the right heart, it is due to the fact that the more virulent the organism, the less necessary the violence of the impact necessary to secure its lodgement. He points out that patients with auricular fibrillation rarely develop endocarditis, because blood drools through the valve concerned.

Boldero and Bedford (1924) think that the access of arterial blood to the right heart in congenital cases with patent septa may explain the unusual frequency of dextral endocarditis in this type of case, but in our case both sides were affected, though there was no septal defect. A possible explanation of this is that put forward by Hadfield and Garrod (1942): they postulate that when the pressure of any chamber is raised above the normal, this predisposes to trauma of the related valves and to endocarditis, so that when for example mitral incompetence is present, thus raising the pressure in the pulmonary circuit, right sided involvement is a

frequent finding. Von Glahn and Pappenheimer (1935) claim that the disease attacks valves, the seat of recent, not old, rheumatic infection, as is usually thought. In this case there was no evidence of any rheumatic infection of a valve, nor was there any rheumatic history, recent or remote. Another well-known important point, is that the *Strept. viridans* will attack valves that are congenitally malformed, such as bicuspid aortic valves. In this case there were no signs of congenital abnormality.

What is the source of infection in this disease? Horder (1908) showed that infective endocarditis was pre-eminently a streptococcal disease (for streptococci occurred in 66 per cent of his series of 40 cases) and that the types most often found on blood culture were those present in fæces and normal saliva, i.e. *S. fæcalis* and *S. salivarius.* He also pointed out the absence of any visible focus of infection and later showed that pressure on an apical root abscess forced the contents of the abscess into the lymphatics (quoted by Hadfield and Garrod, 1942). This work has been confirmed by Okell and Elliott (1935), who performed a series of blood cultures on patients undergoing dental extraction, and found bacteræmia in 75 per cent of those examined. In their analysis they agree with Horder that the vast majority of streptococci in infective endocarditis are of the salivary or *S. viridans* type, a fact which has been amply confirmed since. These abound in the mouth and its neighbourhood, especially in the condition of oral sepsis. In 110 cases of pyorrhœa, 12 were found in their series to have a streptococcal bacteræmia at the time of examination, irrespective of operative procedure; i.e. in persons with severely septic mouths, streptococci usually of the viridans type may enter the blood-stream in the absence of any obvious trauma. This leak is obviously not a blood infection and will depend on the rapidity of the phagocytic clearance of the blood-stream, and though of little account in the normal person, may determine an endocarditis in those with diseased or malformed valves. In our case, the man had a mouth full of foul teeth, but unfortunately no culture was made of the organisms therein. The amount of septic absorption taking place must have been on a considerable scale and probably *S. viridans* was present in the gums.

Pus formation is usually not a feature of this disease. It occurred in two places, the pericardium and cerebral meninges both showing *S. viridans* on direct examination—in this case, probably as a terminal event owing to the intense final bacteræmia and pyæmia.

At the time of treating this case, penicillin was not available, and it, therefore, illustrates the uselessness of sulphonamide therapy alone.

A note on the diagnosis of a tricuspid lesion *per se*, might not be out of place. The characteristic features described are the intense venous engorgement with systolic pulsation of the deep and superficial veins, *especially the jugular*, due to the large rise in the systolic pressure in the right auricle, and the presystolic and systolic murmurs with reduplication of the second sound at the xiphisternum. Van Bogaert and Mortelmans (1942) emphasize the importance of the *persistence* of these signs in any case, while Bramwell and King (1942) stress the fact that the P wave of the cardiogram is of unusually high voltage. Finally, in cases with combined mitral and tricuspid lesions, Röslers' sign is valuable, namely, radiography of the heart showing a lack of dilatation of the left auricle due to the tricuspid lesion decongesting the pulmonary circuit, and so relieving the burden of the auricle.

SUMMARY

A case of endocarditis lenta affecting the aortic and tricuspid valves, in a man of 50 years, is described.

The dangers of oral sepsis in cases with known heart disease are stressed.

In the diagnosis of the individual lesion, the significance of the persistence of systolic and presystolic bruits at the xiphisternum is emphasized.

I would like to thank Dr. Benton, Acting Medical Superintendent, City Hospital, Nottingham, and Dr. Johns, the Hospital Pathologist, for the pathological findings.

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ABSTRACTS OF CARDIOLOGY

The Construction of the Cardiac Vector. R. F. HILL. *Amer. Heart J.*, **32**, 72–81, July, 1946.

This article should be helpful to workers new to the field of cardiac vector study. The frontal plane cardiac vector may be constructed by measurements of potential differences in leads I, II, and III, or by obtaining the potential values at the right arm, left arm, and left leg by means of Wilson's unipolar lead. In the first method, directions are obtained from the sides of Einthoven's triangle or from their representation in Bayley's triaxial system; in the second method they are derived from axes joining the centre of Einthoven's triangle to its apices. If the scalar measurements in method I are called e_1, e_2, and e_3 respectively, and those in method II are called V_R, V_L, and V_F, then we have the equations $e_2=e_1+e_3$, and $e_2=V_F-V_R$; but the author points out that this last relationship is invalid when the measurements are turned into vectors, and shows that under these circumstances $V_L-V_R=e_1\sqrt{3}$, $V_F-V_R=e_2\sqrt{3}$, and $V_F-V_L=e_2\sqrt{3}$. Incidentally it is emphasized that the equation $e_2=e_1+e_3$ has nothing whatever to do with Einthoven's triangle, but holds good for the relationship between any three points in an electrical field when considered as a closed loop, and when the galvanometric connections are arranged as they are in electrocardiography. *Paul Wood*

The Effect of Theophylline Aminoisobutanol on the Circulation in Congestive Heart Failure. F. U. STEINBERG and J. JENSEN. *J. Lab. clin. Med.*, **31**, 857–865, Aug., 1946.

The effect on the circulation of theophylline aminoisobutanol (0·24–0·48 g. intravenously) and (in a smaller number of cases) of aminophylline and sublingual glyceryl trinitrate was studied. The venous pressure was followed for 1 or 2 hours and the circulation time measured frequently, generally with "decholin." In nearly all of 14 cases tested there were falls in venous pressure and reductions in the circulation time. Considerable variations in the venous pressure were noted. There was generally an immediate rise after venepuncture and after coughing, vomiting, or straining. Relaxation or sleep caused a fall. The injection of theophylline usually caused an abrupt fall; sometimes this reached its lowest almost at once; always within half an hour. In the cases where the dose was 0·48 g. the fall varied between 8 and 77 with an average of 37 mm. of water. Aminophylline (0·48 g. intravenously) and nitroglycerin (0·6 mg. sublingually) were equally effective, but the fall seemed to be a little more lasting with aminophylline. In a few patients there was no fall with any of these drugs and the results were rather inconstant from day to day. The fall was not accompanied by any change of plasma volume. The average circulation time was shortened by 10 seconds: the duration of the effect was not measured carefully but it seemed to be about an hour.

The authors conclude that theophylline has a useful place in the treatment of congestive failure, but mainly in emergencies because the effect begins to wear off quickly. *Maurice Campbell*

Observations on the Effect of Theophylline Aminoisobutanol in Experimental Heart Failure. J. R. SMITH and J. JENSEN. *J. Lab. clin. Med.*, **31**, 850–856, Aug., 1946.

Following the demonstration of Steinberg and Jensen that in patients with congestive heart failure theophylline aminoisobutanol lowered the venous pressure and shortened the circulation time, the authors have used the heart–lung preparation of the dog to investigate this action further. Heart failure was produced by adding 0·20 per cent chloral hydrate to the perfusing fluid (generally 0·8 g. in all). The subsequent addition of theophylline aminoisobutanol (0·06 g.) to the perfusing blood generally stimulated the myocardial contractions with restoration of function, so that pulmonary œdema and congestion were removed promptly (usually within 1 minute). Dilatation of the heart was overcome and the cardiac output increased. The strength of the cardiac beats was increased, and this did not seem to depend on any increased coronary arterial flow. It is concluded that the clinical benefit previously observed was due to improved myocardial function and pulmonary flow and that peripheral vasodilatation might also help in producing the improvement. *Maurice Campbell*

Fluids in Congestive Heart Failure. C. M. LEEVY, J. A. STRAZZA, and A. E. JAFFIN. *J. Amer. med. Ass.*, **131**, 1120–1125, Aug., 1946.

Some clinicians are now departing from the practice of restricting fluid intake in congestive heart failure; this communication advocates giving the patient as much fluid as he desires, or even forcing fluids. It is believed that restriction of intake to 2 pints (1·1 litre) daily or less may lead to dehydration of the tissues and toxic effects such as pyrexia and mental changes. A high fluid intake is held to facilitate the excretion of waste products by the congested kidney.

The authors report the results of an investigation of 122 patients with congestive failure to determine

the relative advantages of restricted fluids, fluids *ad libitum*, and forced fluids. All received a special diet containing little salt, while other routine methods of treatment for congestive failure were the same in the 3 groups. Mercurial diuretics were used " only when the degree of œdema was a major source of discomfort." Of those on restricted fluid (not more than 1200 ml. daily) and those on forced fluids (up to 7600 ml. daily) about equal proportions (one-sixth of the total) were unable to adhere to the regime because of the ensuing discomfort Failure symptoms disappeared in the same time, after about 10 days, in each of the 3 groups. Of 36 patients in the restricted fluid group 1 developed symptoms attributed to dehydration. When fluids were forced no adverse effects were noted on dyspnœa, heart rate, circulation time, venous pressure, or cerebral function. The regime of fluids *ad libitum* was best tolerated. [These results suggest that fluid limitation in congestive failure is less necessary than has been assumed, and that it may on occasion be harmful; but they do not show dehydration toxaemia to be other than an exceptional result. The special diet used would be difficult to arrange in home treatment.]

Harold Cookson

Circulatory Failure. [In English.] J. McMICHAEL. *Schweiz. med. Wschr.*, **76**, 851–857, Sept., 1946.

The " back-pressure " theory of cardiac failure, based on the idea that the veins are passive tubes, becomes obsolete with the knowledge that alterations in venous tone and calibre affect cardiac output. Starling showed from heart-lung preparations that the venous inflow directly governed the output of the heart; as the filling pressure rose the output increased, but when a certain point of distension was reached further stretching of the heart lowered its output. In early failure the heart's output is not significantly reduced, though its capacity for improvement is diminished. Output drops later in failure. Accurate estimations of output and filling pressure by Cournand's method of right auricular catheterization, performed without mishap in over 500 cases since 1941, have shown that in valvular and hypertensive heart disease with failure the rise in venous pressure is not the back-pressure effect of a falling output but a compensatory mechanism to maintain an optimal output. The first rise in venous pressure occurs when the output is only slightly below normal. As failure advances the venous pressure rises and output falls to 3 litres per minute (normal 5·3).

Digitalis is found to reduce the venous pressure; this is followed in the normal heart by a fall in output and in the failing heart by a rise. Similar results are obtained by venesection, irrespective of the ventricular rate, which suggests that the value of digitalis lies primarily in its action on venous pressure rather than in its slowing effect on heart rate in auricular fibrillation. That digitalis takes a venous overload off the heart is supported radiologically by evidence of reduction in heart size, and clinically by the equally good results of digitalization in failure with normal rhythm. Anæmia, emphysema, thyrotoxicosis, beriberi, traumatic arteriovenous aneurysm, and Paget's disease are characterized by high cardiac output. In severe anæmia blood volume is always reduced, indicating that the venous congestion is due to compensatory increase in venous tone and reduction of vascular bed. In anæmia with hæmoglobin below 30% the output is doubled, venous pressure high, and pulse fast. These patients are already in a critical condition with venous congestion and œdema, and transfusion may be dangerous by further increasing venous pressure, unless given slowly with digitalis. Digitalis alone, by reducing venous pressure, upsets this compensatory equilibrium and is, therefore, dangerous in heart failure from anæmia, emphysema, and acute or chronic cor pulmonale. For similar reasons it is useless in shock. In Paget's disease, where the effect of the increased skeletal circulation resembles arteriovenous aneurysm, failure occurs with high output and raised venous pressure. In pericardial tamponade the rise in venous pressure is again compensatory to maintain an effective cardiac filling pressure.

Peripheral circulatory failure (shock) is no longer believed to be due to pooling of blood in the veins or to hæmoconcentration. With hæmorrhage the effective volume of circulating blood is reduced and the heart's filling pressure and output cut down, but peripheral resistance is raised. The lowered blood pressure is due more to lack of vasoconstriction than to reduced cardiac output, which seldom falls below 3 litres per minute. Later vaso-vagal fainting may occur (with slow pulse and fall in blood pressure) from sudden vasodilatation of arterioles in skeletal muscles. Overwhelming bacterial toxæmia reduces both venous pressure and cardiac output, though suprarenal cortical damage may contribute. Further work on non-surgical shock suggests that peripheral vasodilatation and high cardiac output exist in early diabetic acidosis.

[The direct clinical application of some of the methods discussed in this paper have to be confirmed. In the failing heart the importance of the coronary circulation and of the balancing mechanism between right- and left-sided stress are additional factors of importance that call for consideration.]

J. L. Lovibond

Experiences with Dicumarol in the Treatment of Coronary Thrombosis with Myocardial Infarction. I. S. WRIGHT. *Amer. Heart J.*, **32**, 20–31, July, 1946.

Dicoumarol was used in cases of coronary thrombosis. The indications for its exhibition were: (1) repeated minor attacks of thrombosis; (2) embolic phenomena indicating intracardiac thrombosis. The procedure was as follows. The prothrombin time was estimated (13 to 14 seconds is normal). If normal or lower, 300 mg. of dicoumarol was given by mouth. Each morning the prothrombin time was

determined again, and afterwards a further dose of 300 mg. was given until the time was 30 seconds, or 100–200 mg. if between 30 and 35 seconds. When over 35 seconds the drug was discontinued until the time had fallen to 30 seconds. Smaller doses were then resumed (100 mg.). The course lasted 30 days. Hæmorrhagic manifestations occurred with the prothrombin time at 60 seconds, and were relieved by 300–500 ml. of fresh blood, and by vitamin K (menadione bisulphite) 64 mg. in 1 to 4 doses.

The results seemed to show a diminished mortality in the 76 cases observed. There was no unfavourable effect on the heart. *Terence East*

Testosterone in Angina Pectoris. E. B. LEVINE and A. L. SELLERS. *Amer. J. med. Sci.*, **212**, 7–11, July, 1946.

Twenty-four male patients, average age 56 years, were treated with androgens. The authors conclude from this series that androgens are ineffective in the treatment of angina, though they consider that their results show that testosterone, especially in the form of testosterone propionate by injection, is of definite value in relieving the chest discomfort of the climacteric or of cases of neuro-circulatory asthenia in men of the angina age group. *P. M. F. Bishop*

Congenital Aortic Atresia. N. H. ISAACSON, S. D. SPATT, and D. M. GRAYZEL. *J. Pediat.*, **29**, 222–225, Aug., 1946.

Pheochromocytoma and Chronic Hypertension. D. M. GREEN. *J. Amer. med. Ass.*, **131**, 1260–1265, Aug., 1946.

A case of pheochromocytoma is reported and 50 additional records from the literature are discussed. In cases where the paroxysmal features are overshadowed there is a remarkable resemblance to idiopathic hypertension. After the removal of an encapsulated renal tumour all the symptoms improved. In an analysis of 50 cases from the literature it is found that the majority are chronically hypertensive, and only a minority manifested intermittent hypertension. Of this latter group surgical removal of the tumour interrupted the disease in 12 of 14 patients. It is suggested that all patients with functioning pheochromocytoma will progress to a stage of chronic hypertension if they live long enough, and evidence of cardiovascular and renal disease then becomes common. In the interval between paroxysms in the intermittent type, kidney dysfunction is recorded in only 4 of 14 cases. In 22 cases in which the symptoms had progressed to a state of chronic hypertension, and with a mean duration of 4 years, there was a uniform fall in blood pressure after operation, and a retrogression of cardiovascular-renal abnormality. *G. Hesketh*

Temporal Arteritis. D. A. DANTES. *J. Amer. med. Ass.*, **131**, 1265–1269, Aug., 1946.

The author reports a case of temporal arteritis, and discusses 27 unquestionable cases recorded. The youngest was 55 years of age, the average age being 65 years. Pain is prominent, commonly in the temporal region. A temperature persists for several months, and there may be malaise and sweats. Ocular disturbance is common, œdema, exudates, retinal hæmorrhages, and thrombosis of the retinal artery all occurring. Symptoms suggesting cerebral involvement have been observed. Characteristically a segment of one or both temporal arteries is prominent, indurated, nodular, and tender, and pulsation may be lost. Adjacent arteries may be affected. Complete clinical recovery occurs in the majority of cases, but permanent visual impairment may result from the retinal lesions. *G. Hesketh*

Potential Variations of the Right Auricular and Ventricular Cavities in Man. H. H. HECHT. *Amer. Heart J.*, **32**, 39–51, July, 1946.

Intracardiac catheterization has made it possible to record, by means of an electrode in the right side of the heart, the changes in electrical potential in the venæ cavæ, right auricle, and right ventricle in the human subject. It has been supposed that the unipolar lead (VR) from the right arm recorded the potential variations within the cavities of the heart. In this investigation 5 cases were studied. Two had right bundle-branch block, 1 had left bundle-branch block, and 2 had left ventricular enlargement. The position of the electrode was located by fluoroscopy.

There were three interesting observations: (1) At high auricular levels there are large predominantly negative auricular deflections. Endocardial auricular deflections are always biphasic and show a QRS type of deflection and are often followed by a T wave. At the lower levels a positive wave, which is called PR (like R in QRS), appears. (2) Ventricular complexes from the junctional area show negative deflections in a normally activated heart, and in left bundle-branch block. The deflections are positive in right bundle-branch block. (3) Ventricular complexes recorded at the higher auricular levels are different from those recorded at the lower levels and from the cavity of the right ventricle. They resemble those of the unipolar lead on the right arm (VR). In the auricle there is an area of primary and persistent electro-negativity which presumably corresponded to the site of the pacemaker away from which impulses spread, hence the negative sign. Records from the right ventricular cavity in left bundle-branch block do not differ from those in normals, for the left-side lesion does not affect the polarization of the right side. When there is right bundle-branch block the right ventricular endocardial curve is positive. This is due to the fact that the septum and right ventricular cavity are activated from the left side and so a layer of positive charges faces the right ventricular cavity.

These observations are in accord with the new nomenclature of bundle-branch block, and agree with the assumption that the action currents in the heart muscle are to be regarded as an electrical " source " (positive) followed by an electrical " sink " (negative

The ventricular deflections from the higher auricular level differ from those of the right ventricular cavity because they represent the combined changes in the two ventricles together. When activation is normal these are negative. Such are the deflections of the right arm unipolar lead. If there is left bundle-branch block the right ventricular negativity will predominate. In right bundle-branch block the initial negative deflection is derived from the left ventricle but the broad positive deflection from the right ventricular cavity. [It would have been interesting to have had some normals.] *Terence East*

The Influence of Drugs on the T Wave of the Electrocardiogram after Exercise. (Über den Einfluss vegetativer Pharmaka auf den Ablauf der T-Zacken-Veränderungen im Arbeits-Elektrokardiogramm.) A. WALSER. *Cardiologia*, **10**, 231–250, 1946.

Slight exertion and severe exertion were found to influence the height of T in opposite senses. Severe exertion caused an initial increase of T followed by a prolonged decrease. Slight exertion caused an initial decrease of T followed by a prolonged increase. The previous injection of sympatol-atropine accentuated the initial and the late changes in the height of T after severe exertion. Previous injection of physostigmine-gynergen accentuated only the initial increase in T after severe exertion but caused a more rapid return to the previous level. Neither sympatolatropine nor physostigmine-gynergen caused a decisive difference in T-wave behaviour after slight exertion. The author concludes that parasympathetic excitation leads to an increase in the height of the T wave.

G. Schoenewald

Heart Disease in Pregnancy. W. B. STROMME and K. KUDER. *Amer. J. Obstet. Gynec.*, **52**, 264–272, Aug., 1946.

Stromme and Kuder review the previous publications on this subject from the department and then analyse a further 720 cases of heart disease in pregnancy. They show that maternal mortality from sepsis and hæmorrhage have so far decreased that in the series analysed heart disease was the leading cause of maternal mortality. Rheumatic disease was responsible for 91 per cent of the heart cases, congenital lesions accounted for 4 per cent and hypertensive disease for 2 per cent. The authors stress the importance of evidence of decompensation or fibrillation. This is claimed to be often a legitimate indication for termination of pregnancy and sterilization.

The importance is stressed of careful supervision of all cases and treatment of selected ones in hospital. Heart disease was detected in 3 per cent of all obstetric cases analysed. Therapeutic abortions were performed in 8 per cent, and for delivery forceps were used more and Caesarean sections less than in the previous series reported from the same department. The total mortality rate was 12 per 1000 cardiac cases and the mortality in the group admitted as emergencies was 7 times that of the group which received antenatal care. *J. Stallworthy*

The Clinical Use of Cytochrome C in Patients with Intermittent Claudication. S. PROGER and D. J. DEKANEAS. *Bull. New Engl. med. Center*, 8, 145–147, Aug., 1946.

The improved utilization of oxygen in the tissues resulting from the use of cytochrome C, on which the authors had previously reported (*J. clin. Invest.*, 1945, **24**, 864), led them to examine its effects in cases of intermittent claudication. Cytochrome C was given intravenously in doses of 50 mg. daily to 13 patients suffering from intermittent claudication due to thrombo-angiitis obliterans or arteriosclerosis. Of these, 3 showed no improvement, 3 definite but moderate improvement, and 7 striking improvement. This was assessed by means of exercise tolerance tests, involving stair climbing and level walking. Controls were made with the injection of an inert solution similar in colour to that of cytochrome. The characteristic response was increase of exercise tolerance, which reached a maximum after 10 injections and was maintained for a long time after the injections had been discontinued, in 1 case almost a year. *B. Samet*

The Effect of Meals on the Electrocardiogram in Normal Subjects. E. SIMONSON, H. ALEXANDER, A. HENSCHEL, and A. KEYS. *Amer. Heart J.*, 32, 202–214, Aug., 1946.

The effect of meals on the electrocardiographic records in 12 normal adults was studied and the results were analysed statistically. An hour after moderate meals significant changes were observed—increase of heart rate, K_{QT} and QRS amplitude, decrease of T wave, duration of mechanical systole and QT interval, and left axis shift of the T axis. These changes were independent of the proportion of fat in the meal. *W. J. H. Butterfield*

Changes in the Cardiovascular System in Scrub Typhus in Early Convalescence. W. LIKOFF. *Amer. J. med. Sci.*, **211**, 694–700, June, 1946.

The authors have investigated 100 Service patients in the convalescent stage of scrub typhus. Symptoms relating to the cardiovascular system, including tachycardia at rest, dyspnœa, præcordial pain following exercise, and syncope, were present in 30 per cent of the cases, and in only 2 of these were average daily pulse rates of under 100 recorded.

In the asymptomatic group—70 cases—only 4 patients had daily pulse rates of over 100. No evidence of organic valvular disease or cardiac failure was noted in any of the cases. Ten patients—all in the symptomatic group—gave electrocardiographic abnormalities. Three showed persistent bundle-branch or intraventricular block. Transient changes recorded included delayed A-V conduction, negative T waves in two or more leads, and slurring of the QRS complex without prolonged duration.

A. Henderson-Begg

The Incidence of Palpable Dorsalis Pedis and Posterior Tibial Pulsations in Soldiers. J. J. SILVERMAN. *Amer. Heart J.*, **32**, 82–87, July, 1946.

The average age of the 1014 soldiers studied by one observer was 20, and 90 per cent were under 22. Absence of pulsation in the dorsal artery of the foot and in the posterior tibial together on the same side occurred in 0·5 per cent; posterior tibial pulsation was absent on one side in 5·6 per cent, dorsalis pedis in 25 per cent. Both posterior tibials were impalpable in 1·7 per cent, and both dorsal arteries of the foot in 7·5 per cent. There was a significant difference between white and negro soldiers in these respects. Among the white men one or other posterior tibial artery could not be felt in 2 per cent, and one or other dorsal artery of the foot in 27·1 per cent; whereas among the negroes these figures were 8 per cent and 6·6 per cent respectively.

[No precautions against the effects of cold, emotion, or other factors are described.] *Paul Wood*

Cor Pulmonale in Ankylostoma Infection. E. GARCÍA CARRILLO. *Arch. Inst. Cardiol. Méx.*, **16**, 154–158, May 31, 1946.

Five cases in which the patients died from anæmia, ankylostomiasis, and multiple pulmonary emboli are presented with brief clinical and pathological findings. Both peripheral phlebitis of infective origin and peripheral circulatory stasis give rise to repeated pulmonary emboli. These factors combined with the poor nutritional state and anæmia of the maiority of these patients are held sufficient to account for the heart failure and subsequent fatal issue.

W. T. Cooke

Acute Pericarditis in Young Adults. R. M. NAY and N. H. BOYER. *Amer. Heart J.*, **32**, 222–223, Aug., 1946.

Forty-six cases of pericarditis occurring in soldiers, aged 18 to 37, were investigated by the authors at one of the American army rheumatic fever centres. The diagnosis was based on clinical findings—præcordial or substernal pain, pain on breathing, swallowing, and twisting the trunk, pain worse when lying prone, the presence of friction rubs, radiological evidence of effusion, and electrocardiographic changes. The patients could be divided into 3 groups: (1) 25 patients in whom the pericarditis was associated with signs and symptoms of rheumatic fever; (2) 15 patients in whom the lesion was of undetermined aetiology; (3) 6 patients in whom it was associated with other diseases, such as aneurysm or pleural effusion.

The leads studied were the standard limb leads and the apical lead, IVF. Elevation of S–T segments, in most cases in more than 1 lead, occurred during the first 10 days after the onset of pericarditis in more than half of the patients seen early. There was no reciprocal depression of S–T segments in leads that did not shows S–T elevation. In 41 cases there was striking nversion of T waves and in more than half the cases the T waves were negative, diphasic, or iso-electric in all 4 of the leads. These inversions were usually noted 5 days to 3 weeks after the onset of the disease and might persist for a few days or many weeks. These changes are thought to be highly specific, but repeated electrocardiograms are necessary to detect them. *E. B. G. Reeve*

Foreign Bodies in and in Relation to the Thoracic Blood Vessels and Heart. III. Indications for the Removal of Intracardiac Foreign Bodies and the Behaviour of the Heart During Manipulation. D. E. HARKEN and P. M. ZOLL. *Amer. Heart J.*, **32**, 1–19, July, 1946.

This article describes the removal of 26 pericardial and 13 intracardiac missiles. The reasons for operation are held to be: (1) prevention of embolism of the foreign body or associated thrombus; (2) reduction of danger of bacterial endocarditis; (3) prevention of recurrent pericardial effusion; (4) diminution of the incidence of myocardial damage. It is most important to locate the foreign body accurately and plan the operation so that the maximum facility of exposure is obtained. The heart tolerates dislocation badly. The ventricles may dilate, and interference with the outflow of blood may lead to circulatory collapse. Various arrhythmias, especially showers of extrasystoles, were noted. Bundle-branch block may occur. The surface of the heart must be kept moist. Suturing and superficial manipulation were well tolerated. Intracardiac manipulations were less well borne. Location of fragments is difficult, and many thought to be in the heart were really outside it.

Terence East

Ligation of the Ductus Arteriosus. A. R. GILCHRIST *Edinb. med. J.*, **53**, 346–354, July, 1946.

The persistence of a patent ductus arteriosus in extrauterine life is known to carry with it certain severe complications in a proportion of cases. Infection with *Streptococcus viridans* leading to infective endarteritis and septic emboli is a condition of the gravest severity, and a varying amount of disability may result from the interference with ordinary circulatory mechanics. Both these complications can be overcome by occlusion of the ductus surgically.

The mechanical effects of a patent ductus are due to the fact that the pulmonary artery has to receive blood from both the right ventricle and the higher-pressured aortic stream via the ductus. The output of the left ventricle is thus stressed unduly to the extent by which it loses blood through the ductus. This effect can be observed under the radiological screen, when the forcible contraction of the left ventricle and excessive pulsation of the pulmonary artery may be obvious. The pulmonary artery may also be prominent and the vascular fields of the lung increased. Clinically the characteristic murmur is usually present, but it may not attain its continuous quality for some years. Below the age of 5 the signs are more equivocal and other signs, as mentioned

above, should be sought for. There is, in addition, the increased pulse pressure, which may be very noticeable after exercise. The fall in diastolic pressure following exertion is quickly restored, but when it can be recognized is a valuable diagnostic sign. Infection in the pulmonary artery develops at an area opposite the ductus entrance. Vegetations form and as they fragment are carried into the lungs as emboli. Radiologically, patchy opacities appear in the lung fields, and a positive blood culture is often obtained. Prolonged sepsis leads to cardiac enlargement with congestive failure.

Three cases of well-established infective endarteritis were submitted to operation; there were 2 fatalities from massive pulmonary collapse and 1 dramatic recovery. The author insists that "surgical ligation in the infected case is the only treatment to consider," and early diagnosis is of the greatest importance. Every case of known patent ductus with an unexplained pyrexia should be suspect.

In non-infected cases the reasons for surgery should be considered under several headings: (1) restoration of normal circulation and improvement of development, (2) prevention of infection, (3) prevention of later circulatory incapacity and congestive failure. A series of 36 cases in this class was studied, and 16 were operated on. In the surgical ligation series there were 2 deaths, 1 following a repeat operation (the ductus having re-canalized after original occlusion with catgut ligatures). Of the remainder there was 1 instance of apparent re-canalization and 2 of partial, ductus closure; all other cases show very satisfactory results.

The choice of age for operation, in the absence of infection or cardiac symptoms, lies between 7 and 10 years. Over the age of 20, operation should be reserved for cases that show definite symptoms or signs of disability. The operation is one which requires the specialized team-work of thoracic surgery. Complications in the form of hæmorrhage, pulmonary collapse, pleural effusion or infection may occur, but in the hands of experienced surgeons are rare.

T. Holmes Sellors

Acute Rheumatism. J. A. Glover. *Ann. rheum. Dis.*, **5**, 126–130, June, 1946.

The incidence of acute rheumatism among trained troops has always been below expectation, in spite of the rigours to which they have been exposed. But it does occur in the form of "barrack epidemics" among recruits crowded into training centres. The author tabulates the estimated incidence of rheumatic fever among troops engaged in the Crimean, American Civil, South African, and Great Wars, and shows that there has been a steady decline in incidence and severity of the disease. He writes: "This astounding fact—that in the wet, the mud, and the stench of the trenches in Flanders in 1915 acute rheumatism was much less prevalent than in the high and magnificent climate of South Africa—seem to show that the disease had already begun its long decline in incidence and severity" Such a decline has been found in civilian as well as in military medicine. In 1937 the death rate from rheumatic fever was less than a quarter of that in the period 1891–1900. It is claimed that the period between the two world wars was noteworthy in the history of rheumatic fever, for the decline in incidence of the disease, for the inception of systematic effort to prevent its ravages, and for the support for the theory that it is due wholly or in part to infection by the *Streptococcus pyogenes*.

The theory of streptococcal responsibility for rheumatic fever has been strengthened by the "barrack epidemics"; these occur when adolescents are collected and crowded together, and present a regular cycle in which an epidemic of streptococcal tonsillitis is followed after a latent interval by an outbreak of rheumatic fever. Recruits are vulnerable when exposed to unaccustomed training and fresh strains of streptococci. In these epidemics there is a high carrier rate for the streptococcus. The author quotes a number of reports of barrack epidemics, and emphasizes the damage they do among recruits for the Services, so many of whom, once they have acquired the infection, have to be "invalided out".

The war of 1939–45 affected the civilian population to an unprecedented extent, but nevertheless the decline in incidence of rheumatic fever continued and reached a new low level in 1942, when the crude all-age death rate sank to 12·1 per million—scarcely one-half of what it was in 1934. Figures are given of the decline in incidence in Cardiff, Bristol, Leicester, and Glasgow. Military experience showed a similar decrease in the incidence and severity of cases of rheumatic fever. A comparison is made of the numbers of Service patients treated in military and E.M.S. hospitals, and the proportion of patients suffering from rheumatic fever among all those with "rheumatism" appeared to be approximately the same in both types of hospital. It seems that the number of men invalided from the Services for rheumatic fever has steadily declined through recent wars.

The author discusses chemoprophylaxis, but points out that good ventilation and the avoidance of overcrowding are still the most important methods of preventing outbreaks of streptococcal disease. He quotes Cruickshank (*Mon. Bull. Min. Hlth.*, 1946, 5, 144), who says that while sulphadiazine prophylaxis seemed to help to control streptococcal epidemics, it had an unhappy sequel in the appearance of sulphonamide resistance in certain strains of the organism, and that prophylactic use of sulphonamide drugs might be limited to children who have had 2 attacks of rheumatic fever or have had 1 attack accompanied by carditis. *W. Tegner*

Laboratory and Clinical Criteria of Rheumatic Carditis in Children. L. M. Taran. *J. Pediat.*, 29, 77–89, July, 1946.

The essence of this paper is an assessment of the value of the various diagnostic criteria as a measure of continued activity in rheumatic carditis.

A group of 200 boys and girls, ranging in age from 6 to 14 years, was studied. They were observed from the beginning of an attack of rheumatic carditis to the end of the active process and for at least 6 months after this. The only treatment was good nursing, balanced diet, and moderate amounts of synthetic vitamins. Occasionally the patient was given small doses of salicylates for arthralgia. In each case a complete clinical and laboratory examination was carried out as well as a cardiographic and immunologic investigation.

Leucocytosis.—One out of 10, no leucocytosis at all ; 9 out of 10, continued leucocytosis for the first 2 weeks; 7 out of 10, continued leucocytosis at end of fourth week. At the end of 7 weeks there was no leucocytosis in any case. All cases with a leucocytosis showed clinical rheumatic activity, and 9 out of 10 continued to show clinical rheumatic activity when the leucocytosis had disappeared.

Fever.—Fever as a manifestation of cessation of rheumatic activity is not borne out in this series; the average febrile period was 6 weeks.

A-V Conduction.—In this series a prolonged P–R interval in a rheumatic child in the absence of other laboratory or clinical evidence was not found a safe index of continued rheumatic activity, and the return to a normal conduction time did not always mean cessation of activity.

Pulse Rate.—This was found to be an adequate index of cessation of activity. There was no correlation between pulse rate and temperature. The rate was highest during the first 3 weeks of the disease and was as high as 140, and no case showed a drop to below 100 before the end of the ninth week.

Sedimentation Rate.—This was found not to be as reliable a guide as is commonly believed. Many cases showed a still active rheumatic condition with a normal sedimentation rate. At the end of 16 weeks a number of cases with no clinical evidence of activity had a slightly elevated sedimentation rate.

Weight Gain.—This also was not found to be an index of quiescence. At the end of 7½ months all the children had reached a normal weight gain level, yet 40 per cent still showed mild rheumatic activity.

Hæmoglobin.—All cases showed a moderately severe anæmia to start with, the hæmoglobin ranging from 7 to 9 g.; in 2 children it was as low as 5 g. It was only after 32 weeks that all the cases returned to 12·5 g. or more. However, 40 per cent still showed clinical rheumatic activity after the hæmoglobin was normal.

Vital Capacity.—In this series vital capacity proved to be the most sensitive single index, all the children having a vital capacity of 40 per cent or less below normal for age and body surface. None reached the normal again until 16 weeks after the onset of the carditis. This index also failed as a specific diagnostic measurement because some children continued to have clinical evidence of disease although the vital capacity was normal.

The relation between clinical activity and various tests is indicated in a table. The author points out that active rheumatic disease must be suspected when there is a tendency to fatigue without cardiac insufficiency, emotional instability, and marked pallor. Tachycardia with a tumultuous rhythm, and a gallop rhythm with rapid or slow cardiac rate are looked upon as evidence of rheumatic carditis, and their absence as auscultatory evidence that carditis is at an end. However, the author finds that these criteria are inadequate in diagnosing mild smouldering carditis. *Richard Sands*

Significance of Downward T Waves in Precordial Leads of Normal Children. E. GOLDBERGER. *Amer. J. Dis. Child.*, **71**, 618–621, June, 1946.

Goldberger took electrocardiographs in 50 children, aged 5 to 11 years, who were regarded as normal from the cardiac point of view. He used a unipolar præcordial electrode in 6 positions from the right of the sternum to the mid-axillary line, i.e. leads V_1–V_6. In 9 children (18 per cent) T was inverted in lead V_4—i.e. with the electrode in the fifth left interspace in the mid-clavicular line. He found that when the QRS complex shows an RS pattern, which is usual when the electrode is placed to the right of the left mid-clavicular line, T may be inverted or upright. But when QRS shows a QR or a QRS pattern, as is usual in leads V_5 and V_6, T is upright. An inverted T in association with a QR pattern is stated to be always abnormal. The RS pattern, with which the inverted T may be associated, is believed to occur when the præcordial electrode is facing the epicardial surface of the right ventricle, and the QR and QRS patterns when it is facing the epicardial surface of the left ventricle: hence the larger area of the præcordium which will normally give an inverted T in the child as compared with the adult, the right ventricle being relatively larger in the child. *Harold Cookson*

Peripheral Blood Flow, Rectal and Skin Temperature in Congestive Heart Failure. The Effects of Rapid Digitalization in this State. H. J. STEWART, W. F. EVANS, H. BROWN, and J. R. GERJUOY. *Arch. intern. Med.*, **77**, 643–658, June, 1946.

This paper describes an attempt to measure the total peripheral blood flow in patients with congestive cardiac failure before and after the intravenous administration of strophanthin-K and digitaline (Nativelle). Fifteen patients were admitted to hospital and placed at complete rest in bed. Fluid intake was limited to 1,200 ml. daily and salt intake to 3 g. Before administration of the drug four sets of observations of rectal and skin temperatures were made from which three control levels of peripheral blood flow could be estimated. Blood pressure, heart rate, basal metabolic rate, circulation time, and venous pressure were also estimated. Beginning 15 minutes after the injection, the authors repeated the observations at 20-minute intervals for 70 to 180 minutes. The data collected both before and after the injections were averaged. Strophanthin-K

was given intravenously in doses of 0·25 mg. except to those patients with mitral stenosis, to whom 0·125 mg. was given. Digitaline (Nativelle) was given in doses of 1·2 mg. Some patients had normal rhythm; others auricular fibrillation.

The average peripheral blood flow for all patients with heart failure was 32 ml. per square metre per minute as compared with 33 ml. for normal subjects. Both rectal temperature and average skin temperature were higher than in normal subjects.

The effect of strophanthin and of digitaline was to increase considerably the peripheral blood flow, to increase the average skin temperature, and to decrease the rectal temperature. The heart rate was slowed, the circulation time shortened, and the venous pressure lowered. The authors point out that other workers have shown that digitalis in heart failure produces a decrease in the size of the heart and an increase in cardiac output. Thus, during heart failure the volume of blood allotted to the peripheral circulation in unit time is in the normal range, but it moves so slowly in a distended vascular bed that it is insufficient to eliminate heat from the body and the rectal temperature rises. After the exhibition of strophanthin-K the peripheral blood flow increases, the skin temperature rises, and the rectal temperature falls. The highest peripheral blood flow following the administration of strophanthin-K occurs after 64 minutes, and that following the administration of digitaline (Nativelle) after 114 minutes. *Geoffrey McComas*

Electrocardiographic Features of Myocardial Infarction as Affected by Involvement of the Septum and by Complete and Incomplete Transmural Involvement. [In English.] H. E. B. PARDEE and M. GOLDENBERG. *Arch. Inst. Cardiol. Mexico*, **16**, 109–130, May 31, 1946.

The post-mortem findings in 12 hearts were correlated with the electrocardiographic findings in leads I, II, III, IV F. Two anterior wall infarcts with septal involvement but without involvement of the sub-epicardial fibres showed a QS deflection (absent R wave) in IV F, a feature usually attributed to involvement of those fibres. The QS deflection was associated with septal involvement, as in 5 anterior wall infarcts (4 with no sub-epicardial involvement) it was absent in the only one without septal involvement. In 3 of the 4 cases without sub-epicardial necrosis, ST- and T-wave changes in the limb leads were similar to those seen after anoxæmia and exercise tests. In the fourth case typical changes of acute anterior infarction were seen in all 4 leads. Two complete posterior wall infarcts with septal involvement had typical acute ST- and T-wave changes in all 4 leads. Two posterior wall infarcts, without sub-epicardial and septal involvement, failed to show typical changes in any lead. Typical ST- and T-wave changes were only found in lesions involving the septum and adjacent anterior or posterior walls. Complete transmural involvement of the posterior wall was the only constant pathological finding in cases with large Q 3.

Of 6 incomplete mural infarcts only 1 had a typical record of anterior or posterior wall infarction.

W. T. Cooke

Coronary Occlusion in Young Adults. Review of Fifty Cases in the Services. M. NEWMAN. *Lancet*, **2**, 409–411, Sept. 21, 1946.

In view of the apparent rarity of coronary occlusion in young adults records were analysed of 50 Service men and women up to the age of 35 who had been invalided with, or had died from this condition. In 39 cases proof of coronary occlusion was obtained at necropsy, and in the surviving cases the diagnosis was supported by the characteristic cardiographic changes. The youngest patient was aged 20, and 22 of the 50 were in their twenties; as in the older age groups, the frequency increased with age. Coronary occlusion appears commoner in males than females in the younger age groups as well as in the older.

The striking feature was the good physical development and nourishment of these subjects; robustly built, they had a tendency to adiposity. Forty-five had been grade I on entry. The heart had been recorded as normal in every case, and all the subjects were apparently in excellent health.

Only 3 showed evidence of hypertension. Previous infection may have been of ætiological significance in a few cases ; 3 gave a history of rheumatic fever, 2 of scarlet fever, and 1 (with marked coronary atheroma) had chronic osteomyelitis; 2, who both survived, had syphilis. In more than half there was no evidence of physical strain before onset, and less than half had done heavy work in their pre-Service occupation.

The 78 per cent mortality, 83 per cent of which was immediate, was surprisingly high, and would appear to indicate a much worse prognosis in younger people. At necropsy the left coronary artery was affected in 17 cases, the right in 5, and both in 16. The findings did not support the view of Leary (*Arch. Path.*, 1941, **32**, 507) that calcification does not occur in the younger age group, and that coronary occlusion is due to sub-endothelial fibrosis with necrosis of the intima leading to thrombosis. Only 2 cases showed fibrotic reaction without calcification; the remaining 37 presented the usual degenerative atheromatous changes of coronary disease in older persons, several with extensive calcification. In 29 of the 39 cases no thrombus was found; half the cases showed recent or long-standing infarcts.

[The findings and conclusions are similar to those of Miller and Woods (*Brit. Heart J.*, 1943, **5**, 101) who, however, noted a striking history of familial " defective tubing."]

E. G. Sita-Lumsden

Haemodynamic Factors and Retinal Changes in Hypertensive Diseases. [In English.] S. BJÖRK. *Acta med. scand.* Supp. 175, 1–165, 1946.

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